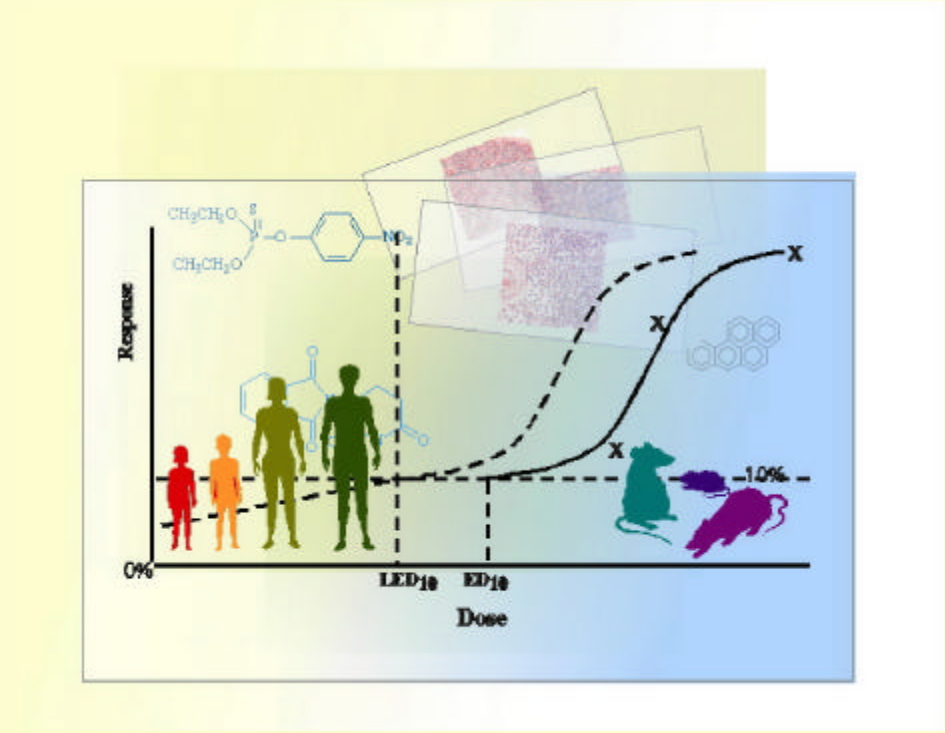
HUMAN HEALTH RISK ASSESSMENT

Fenamiphos



U.S. Environmental Protection Agency
Office of Pesticide Programs
Health Effects Division (7509C)

Julianna Cruz, Risk Assessor
September 2, 1999

HUMAN HEALTH RISK ASSESSMENT

Fenamiphos

Phase 5

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Table of Contents

Attachments:

1. Toxicology Chapter

2. Toxicology Endpoint Selection Document

3. Fenamiphos: FQPA Requirement - Report of the Hazard Identification Assessment Review Committee

4. Hazard Assessment of the Organophosphates: Report of the Hazard Identification Assessment Review Committee

5. FQPA Safety Factor Recommendations for the Organophosphates (A Combined Report of the Hazard Identification Assessment Review Committee and the FQPA Safety Factor Committee).

6. Tolerance Reassessment Summary

7 Codex Harmonization

8 Fenamiphos Anticipated Residues

Introduction

This revised risk assessment for fenamiphos includes the changes made in response to comments received from USDA. The initial risk assessment prepared on May 23, 1994 has been revised and/or updated on October 25, 1995, March 15, 1996, December 23, 1998 and March 29, 1999.

The document submitted on March 15, 1996 incorporated:

- ❖ Mitigation from the registrant lowering the rate and frequency of the applications of fenamiphos;
- ❖ An occupational exposure and risk assessment based on the mitigation;
- ❖ An occupational exposure and risk assessment including inhalation (as it is a newly identified toxicological endpoint of concern);
- ❖ Refined acute dietary exposure and risk analysis;
- ❖ Drinking water exposure and risk analysis;
- ❖ Additional toxicological endpoints for risk assessment; and
- ❖ Newly accepted 21-day inhalation study in rats.

The document submitted on December 23, 1998 included the following:

- ❖ Results of the acute and subchronic neurotoxicity studies;
- ❖ Determination of increased susceptibility to infants and children;
- ❖ Aggregate risk assessment;
- ❖ Alignment of drinking water risk assessment conducted before FQPA with current FQPA drinking water risk assessment policy;
- ❖ Results of a recently submitted (December 1998) Monte Carlo analysis for the acute dietary risk assessment;
- ❖ Revised toxicological endpoints identified by the Toxicology Endpoint Selection Committee (August 8, 1996);

- ❖ Toxicological endpoints identified by the Health Effects Division's Hazard Identification Review Committee (September 19, 1997);

- ❖ Residue chemistry update to include revisions to OPPTS Test Guidelines Series 860 (August, 1996); and

- ❖ Revised occupational exposure based on the registrant's (Bayer Corporation) proposed mitigation techniques in an effort to reduce potential handler and worker exposure (memorandum dated July 21, 1995 from L. Morris/OREB to B. O'Keefe/SRRD) and using the revised toxicological endpoints of concern for handler and worker risk assessment; and

- ❖ Occupational aggregate risk assessment.

The document submitted on March 29, 1999 included the following:

- ❖ Refinement of acute and chronic dietary anticipated residues using Pesticide Data Program (PDP) and FDA monitoring data;

- ❖ Use of 1989-1992 Continuing Survey of Food Intake by Individuals (CSFII) data and DEEM™ dietary exposure software to calculate acute and chronic dietary exposure estimates;

- ❖ A revised FQPA, aggregate risk assessment; and

- ❖ A revised occupational aggregate risk assessment.

This Phase 5 revision includes corrected anticipated residues, revised in response to comments received from various HED Science Advisory Committees (Chemistry SAC and DEEM SAC) and revisions and/or clarifications provided in response to USDA comments. No significant changes to risk estimates presented in the March 29, 1999 risk assessment have occurred. The acute dietary (food) risk estimates increased by 1% (to 27% of the acute Population Adjusted Dose for the U.S. Population and to 68% for non-nursing infants less than one-year old). The chronic dietary (food) risk estimates decreased by 1% (to 4% of the acute Population Adjusted Dose for the U.S. Population and to 14% for non-nursing infants less than one-year old). No changes were required for the drinking water risk assessment.

I. Executive Summary

The Health Effects Division (HED) has evaluated the fenamiphos database. The toxicological database is adequate to support reregistration. Residue chemistry requirements are substantially complete pending submission of confirmatory data. However, additional data are required for certain occupational and nonoccupational exposure scenarios.

Fenamiphos (Ethyl 3-methyl-4-(methylthio)phenyl-1-(methylethyl) phosphoramidate) is an organophosphate insecticide/nematicide. It is labeled for use on terrestrial food, nonfood, and feed crops. All uses appear to be outdoors except for some of the ornamental uses which may be inside of greenhouses. Fenamiphos is also registered for use on golf course turf; therefore there is potential for nonoccupational postapplication exposure. Fenamiphos controls several varieties of nematodes, thrips, beetles, aphids, and root borers.

Applications can be made using ground equipment or chemigation. Additionally, a majority of the available labels preclude the use of any knapsack/backpack type equipment. Application types include: chemigation, soil band treatments, broadcast treatments, in-furrow treatments, soil injection, and spray/foliar treatments.

Hazard Identification

The toxicology profile of fenamiphos demonstrates that fenamiphos, like other organophosphates has anticholinesterase activity in all species tested including mice, rats, rabbits and dogs. Technical fenamiphos is placed in Toxicity Category I for oral and dermal toxicity and in Toxicity Category II for inhalation toxicity. Fenamiphos causes mild eye irritation and therefore is placed in Toxicity Category III. It is not irritating to the skin (Toxicity Category IV) and is not a dermal sensitizer.

Inhibition of plasma, erythrocyte and/or brain cholinesterase (ChE) activity occurs by all routes of exposure (oral, dermal and inhalation) following acute, subchronic and chronic exposures. Following subchronic or chronic oral exposures, dogs were shown to be the most sensitive species with the Lowest Observed Adverse Effect Levels (LOAEL) for ChE inhibition occurring at a dose of 0.03 mg/kg/day. There is no evidence of increased susceptibility to rat or rabbit fetuses following prenatal *in utero* exposure or following pre-/postnatal exposure to rats for two generations. In these studies maternal or parental No Observed Adverse Effect Levels (NOAELs) are lower or equivalent to the developmental or offspring NOAELs. Additionally, there was no evidence for requiring a developmental neurotoxicity study. Based on the hazard and exposure data, the FQPA Safety Factor (10X) for enhanced susceptibility of infants and children was removed for fenamiphos.

Fenamiphos is classified as a Group E chemical based on no evidence of carcinogenicity in two adequate studies in mice and rats. Mutagenicity studies show that fenamiphos is not mutagenic either *in vivo* or *in vitro*. Metabolism studies in the rat indicated no major differences between oral and intravenously administered fenamiphos. Fenamiphos is degraded and/or eliminated within 48 hours postdosing and does not accumulate in tissues. The major metabolites were sulfoxides and sulfates.

Risk assessments were conducted for fenamiphos as follows: acute and chronic dietary as well as short- and intermediate-term occupational dermal and inhalation exposure scenarios. In addition, a nonoccupational risk assessment was conducted individuals who are exposed to fenamiphos while playing golf. The acute and chronic dietary risk assessments capture exposure estimates for the general public whereas the nondietary (dermal and inhalation) risk assessments are for occupational exposures. These risk assessments were based on a common toxicological endpoint (cholinesterase inhibition) observed following oral, dermal and inhalation exposures.

For the acute dietary exposure and risk assessment, the toxic endpoint selected was based on plasma (males and females) and red blood cell (males) cholinesterase inhibition at the LOAEL of 0.37 mg/kg/day in an acute neurotoxicity study in rats. Because the LOAEL was selected an uncertainty factor (UF) of 300 was used in this assessment, which resulted in an acute Population Adjusted Dose of 0.0012 mg/kg.

For the chronic dietary exposure and risk assessment, the toxic endpoint selected was the plasma cholinesterase inhibition at a LOAEL of 0.03 mg/kg/day from a one-year chronic toxicity study in dogs; the NOAEL was 0.01 mg/kg/day. An UF of 100 was used in this assessment which resulted in a chronic RfD of 0.0001 mg/kg/day.

For the occupational short-and intermediate-term dermal exposure risk assessments, the toxicological endpoint selected was plasma, blood, and brain cholinesterase inhibition from a 21-day dermal toxicity in rats at the NOAEL of 2.5 mg/kg/day. Although a dermal absorption factor is not available, it is not required since a dermal dose was used for dermal risk assessments. For short-and intermediate-term inhalation exposure, the toxicological endpoint selected was inhibition of plasma cholinesterase at a LOAEL of 3.5 μg/L from a 21-day inhalation toxicity study; the NOAEL was 0.25 μg/L (0.061 mg/kg/day). A Margin of Exposure (MOE) of 100 is adequate for dermal and inhalation occupational exposure risk assessments.

Exposure Assessments

Dietary Exposure

The main potential routes of exposure to fenamiphos for the general public (nonoccupational exposures) are through food and water. The most refined dietary exposure analysis to date for fenamiphos is presented in this revised risk assessment. The dietary (food) exposure assessments used the consumption data from the 1989-1992 CSFII. Percent of crop treated data supplied by the Biological and Economic Analysis Division (BEAD) in 1999 were used in this analysis. Both acute and chronic anticipated residues were calculated using residue monitoring data from USDA's PDP and the FDA Surveillance Monitoring Program data. PDP data from 1994-1997 and FDA Monitoring data from 1995-1997 were used for all crops having reassessed tolerances. With the exception of three samples (two grape and one strawberry), all 26,619 samples analyzed by PDP and FDA (for the above noted time periods) for fenamiphos and its regulable metabolites had nondetectable residues. Attachment 1 contains a detailed description of how anticipated residues were calculated for various commodities. Emerging policy (as presented at the Tolerance Reassessment Advisory Committee (TRAC) meetings) concerning commodities having all nondetectable residues in monitoring programs dictates that another exposure analysis be conducted assuming zero residues present.

The percent of the Population Adjusted Dose (PAD) occupied for acute or chronic exposure is a measure of how close the exposure comes to the PAD and is calculated as follows: %PAD = [exposure/PAD] x 100. The PAD is expressed as aPAD (for acute exposure) and cPAD (for chronic). In general, as long as exposures represent less than 100% of the PAD, they do not exceed the Agency's level of concern.

Residential Exposure

Although no fenamiphos products are registered for homeowner use, potential postapplication exposures (short-term) could occur following applications to golf course turf. A range-finder postapplication exposure and risk assessment was performed for adult golfers using dislodgeable foliar residue (DFR) values of five percent of the application rate due to an absence of no chemical-specific data for assessing postapplication turf exposures. These DFR values are less conservative than the 20 percent default value, but more conservative than the one-two percent value from the California EPA roller method study. Other exposure assumptions were derived from the draft Residential Standard Operating Procedures (SOPs), December, 1997 version. Risk estimates are expressed in terms of MOE, which is the ratio of the NOAEL selected for the risk assessment to the exposure. For residential populations, MOEs > 100 (*i.e*., 10X for interspecies extrapolation and 10X for intraspecies variability) do not exceed the Agency's level of concern.

Postapplication dermal exposure MOEs for adult and adolescent golfers exceed the Agency's's level of concern (MOE less than 100). For short-term exposures, the dermal MOEs are 78 and 49 for adults and adolescents, respectively. Because the MOEs for adult and adolescent golfers exceed EPA's level of concern, HED assumes that all nonoccupational postapplication exposure scenarios pertaining to golf course turf (*i.e.,* potential toddler dermal and oral exposure) would also exceed the Agency'ss level of concern.

Aggregate Exposure and Risk Estimates

Acute

Acute aggregate risk estimates exceed the Agency's level of concern due primarily to drinking water exposure. Acute aggregate risk estimates are derived using the combined dietary (food and water) exposure. Acute dietary food exposure has been highly refined using probabilistic techniques (Monte Carlo), residue values derived from the USDA PDP and FDA Surveillance Monitoring Program, distribution of residues or anticipated residues calculated from field trial data (only if PDP or FDA data not available), and incorporation of percent crop treated data (as supplied by BEAD in 1999). Food exposure estimates are based on exposure at the 99.9th percentile. For the U.S. Population, the percent of the aPAD occupied is 28% and for the most highly exposed subpopulation, nursing infants less than one-year old, it is 68% of the aPAD. Drinking water levels of comparison (DWLOCs) were calculated using these dietary (food) exposure estimates. If zero residues are assumed, the acute dietary exposure is zero percent of the aPAD.

Based on Environmental Fate and Effect Division (EFED) Tier 1 and Tier 2 modeling for surface water (GENEEC and PRZM-EXAMS), the lowest of the maximal (day 0) estimated environmental concentrations (EECs) for fenamiphos in surface water is 105 ppb (range for four crops was 105 to 651 ppb). This conservative modeling estimate exceeds the DWLOC for adult males and females (37 and 28 ppb, respectively), and the DWLOC for nursing infants less than one-year old, which is 4 ppb. Thus aggregate dietary and surface water risk estimates exceed the Agency's level of concern.

For groundwater, high-quality monitoring data are available for fenamiphos, fenamiphos sulfoxide, and fenamiphos sulfone, which were used to evaluate the acute risks from drinking water. Ingestion of groundwater by children and adult males and females results in exposures that occupy 750%, 170% and 250% of the aPAD, respectively. Adding acute dietary (food) risk estimates to these values would only result in further exceednce of the aPAD, although the contribution of food to the aggregate estimate is small in comparison to the groundwater contribution (approximately 10 fold less).

Short-Term

Short-term aggregate risk estimates exceed the Agency's level of concern. Aggregate risk assessments require that short-term residential exposures be aggregated with chronic dietary (food) and drinking exposures. The calculated MOEs from the residential exposure scenarios alone exceed EPA's level of concern (the short-term MOEs for postapplication dermal exposure of adult and adolescent golfers from fenamiphos-treated golf course turf are 78 and 49 respectively, both below 100). HED anticipates that aggregating exposures from food and water would only result in a risk estimate that would further exceed the Agency's level of concern.

Chronic

Chronic aggregate risk estimates exceed the Agency's level of concern due primarily to drinking water exposure. Chronic aggregate risk estimates are derived using the combined chronic dietary (food and water) exposure. Chronic dietary food exposure has been highly refined using anticipated residues based primarily on PDP and FDA monitoring data and percent crop treated data. Chronic dietary exposure from food alone does not exceed the Agency's level of concern. The percent of the cPAD occupied from chronic food exposure alone ranges from 4% for the U.S. Population to 14% for children 1-6 years old. The chronic DWLOCs for adult males, adult females, and children are: are 3 ppb, 1 ppb, and 3 ppb, respectively.

Based on EFED's Tier 1 and Tier 2 modeling for surface water (GENEEC and PRZM-EXAMS), the lowest of the chronic (90-day) EECs for fenamiphos in surface water is 47 ppb (range for four crops was 47 to 329 ppb). This conservative modeling estimate exceeds the DWLOC for the U.S. Population (which is 3 ppb) and the DWLOC for children 1-6 years old (which is 1 ppb). Thus, aggregate chronic dietary and surface water risk estimates exceed the Agency's level of concern.

For groundwater, high-quality monitoring data are available for fenamiphos, fenamiphos sulfoxide, and fenamiphos sulfone, which were used to evaluate the chronic risks from drinking water. Ingestion of groundwater by children, and adult males and females results in exposures that occupy 1000%, 300% and 300% of the cPAD, respectively. Adding chronic dietary (food) risk estimates to these values would only result in further exceedence of the cPAD, although the contribution of food to the aggregate estimate is small in comparison to the groundwater contribution
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Occupational Exposure

Occupational exposure to fenamiphos residues can occur for pesticide handlers, mixers, loaders, and applicators, and postapplication workers during harvesting activities. The occupational risk assessments are considered to be partially refined because they are based on registrant-supplied data (*i.e.*, acres treated per day) rather than HED default assumptions. As noted previously, dermal and inhalation risk estimates are expressed in terms of MOE, which is the ratio of the NOAEL selected for the risk assessment to the exposure. For occupationally exposed workers, MOEs > 100 do not exceed the Agency'ss level of concern.

Handler Exposure

The results of the agricultural handler assessments indicate that all but two of the potential mixer/loader and tractor-drawn applicator exposure scenarios for a granular formulation have total dermal and inhalation MOEs less than 100 at baseline attire
(*i.e.*, long pants, long-sleeved shirts, no gloves) and therefore, exceed the Agency's level of concern. The two baseline scenarios with total MOEs that do not exceed EPA's level of concern are strawberries and eggplant. The total MOEs are driven by inhalation exposure. Using engineering controls, all of the scenarios evaluated have total dermal and inhalation MOEs that are above 100, and therefore do not exceed the Agency'ss level of concern, except for tractor-drawn granular application to turf (MOE = 44).

The total dermal and inhalation MOEs for all baseline mixer/loader scenarios (groundboom and chemigation) for a liquid formulation were less than 100, and therefore exceed the Agency's level of concern. The total MOEs in these scenarios are driven by dermal exposure. Using engineering controls most of the mixer/loader scenarios evaluated have total dermal and inhalation MOEs that are above 100, and therefore do not exceed the Agency's level of concern, except for 12 commodities (apples, cherries, citrus, nectarines, peaches, grapes, tobacco, pineapples, turf, pome/stone/citrus fruit, kiwi, and ornamental nonflowering plants) where the MOEs range from 37 to 80. The total MOEs for all baseline groundboom applicator scenarios for a liquid formulation were less than 100 (range from 10 to 82), and therefore exceed the Agency's level of concern except for five commodities (beets, asparagus, eggplant, strawberries, and raspberries). The total applicator MOEs are driven by inhalation exposure. Using engineering controls most of the groundboom applicator scenarios evaluated have total dermal and inhalation MOEs that are above 100, and therefore do not exceed the Agency's level of concern, except for eight commodities (apples, cherries, citrus, nectarines, peaches, grapes, tobacco, and turf) where the MOEs range from 53 to 86.

For soil injection, there are no data available.

Postapplication Exposure

To be effective, fenamiphos should be mechanically incorporated or irrigated into the soil immediately after treatment and, with the exception of pineapples, fenamiphos is not directed at foliage (even though foliage may be present during application). Therefore, postapplication exposure is mostly a concern for human activities that may involve contact with the soil after treatment (*e.g.*, applied just prior to transplanting strawberries), and harvesting pineapples. The Registration Standard (1987) indicated that reentry data were required. Approximately one year later, the registrant requested a waiver of the data requirements and of the proposed 48-hour reentry interval for the golf course use. Previously the Agency granted a waiver for both a data requirement and the 48-hour reentry for the golf course use. However, in light of FQPA, the data waiver previously granted for golf courses is no longer applicable. The registrant needs to provide a Turf Transferable Residue (TTR) study for golf course turf to refine postapplication exposure estimates.

There are no chemical-specific exposure data for handling fenamiphos-treated soil; therefore the Agency is requiring data and/or further clarification of the use patterns involving workers handling or working with or in the treated soil which may result in postapplication exposure. These uses are on strawberries, asparagus, ornamental nonflowering plants, ornamental herbaceous plants, sod farm turf, ornamental woody shrubs and vines, and all nursery stock.

The Agency concurred with the registrant, and is requiring a 17-day REI

following foliar applications to pineapple. The Agency's concurrence is based on the registrant's chemical-specific DFR study. With a 17-day REI or more, the harvester/worker's exposure does not exceed EPA's level of concern (*i.e.,* MOE =110). Workers' exposure exceed the Agency's level of concern from the day of application to 16 days after application (MOEs range from eight to less than 100). For all other use sites within the scope of the Worker Protection Standard (WPS) (see PR Notice 93-7) where fenamiphos is incorporated into the soil either mechanically or through watering-in, the Agency is requiring a 48-hour restricted entry interval (REI). During the REI, the Agency will allow workers to enter areas treated with fenamiphos only in the few narrow exceptions allowed in the WPS. The 48-hour REI is being established based on: (1) classification of fenamiphos active ingredient as toxicity category I for acute dermal toxicity; (2) concerns about other adverse effects (cholinesterase inhibition); and (3) the fact that, unlike the foliar application to pineapple, the applications are immediately incorporated into the soil mechanically or through watering-in.

Data Requirements

Product Chemistry Data Requirements

- The registrant must submit: 830.1600 – Description of materials used to produce the product; 830.1620 --Description of production process; 830.1670 – Discussion of formation of impurities; 830.1700 -- Preliminary analysis; 830.1750 -- Certification of ingredient limits; 830.1800 -- Analytical methods to verify the certified limits for the 85% T (EPA Reg. No. 3125-269); 830.1550 – Product identity and disclosure of ingredients for the 72.3% FI (EPA Reg. No. 3125-33);and either certify that the suppliers of starting materials and the manufacturing process for the fenamiphos products have not changed since the last comprehensive product chemistry review or submits a complete updated product chemistry data package. These data are considered confirmatory.

- Data pertaining to the nitrosamine content of some fenamiphos products are outstanding, but is not expected to be of dietary concern since nitrosamines have not been detected in previously submitted studies.

Residue Chemistry Data Requirements

- Storage stability studies with asparagus, bananas, garlic, and the processed commodities of cottonseed and grapes which will be used to fulfill the outstanding requirements for storage stability data on asparagus, bananas, Brussels sprouts, garlic, okra, and strawberries and the processed commodities of cottonseed, grapes, and pineapples. The representative data must be consistent with the storage intervals of commodities from magnitude of the residue and metabolism studies for both the commodities tested and commodities to which these data will be translated. Because all previous storage stability studies for both registered and unregistered commodities provide preliminary evidence of stability of fenamiphos residues in plant commodities, the outstanding data are considered confirmatory and the existing information sufficient to support the magnitude of residue studies and the tolerance reassessments.

- Lack of data regarding fenamiphos residues on cotton gin by-products will not affect the reregistration eligibility, but confirmatory data are required. The registrant must submit six studies reflecting residues of all regulated residues on cotton gin by-products; three trials each must be conducted reflecting harvesting by stripper and picker methods (OPPTS Guideline 860.1500).

- In light of the updated poultry metabolism study and a two-fold reduction in the theoretical dietary burden for poultry based on feed items listed in Table 1, Residue Chemistry Guidelines 860 Series dated August 1996, the Agency has reevaluated the need for additional poultry feeding studies. The use of fenamiphos on poultry feed items is considered a category of 40 CFR 180.6(a)(3); thus, additional poultry feeding studies and tolerances for residues of fenamiphos in poultry meat and eggs are not required (Guideline 860.1480).

- Many of the animal feed items used to estimate secondary residues in livestock commodities are no longer considered significant feed items in the most recent version of the Residue Chemistry Guidelines Table 1, 860 dated, August 1996. Based on these revisions, the reassessed tolerances have been reconsidered, particularly for animal feed items, and meat and milk tolerances are no longer required. Therefore HED now considers this to be a 40 CFR §180.6(a)(3) situation, and that all tolerances for meat and milk should be revoked.

- To assure that illegal residues are not found in rotational crops, and to facilitate inclusion of rotational crop residues in dietary risk assessment, the registrant must either: (1) amend product labels to include an eight-month plantback interval so that residues of fenamiphos and its regulated metabolites will not be found in rotational crops, or (2) based on the limited field trial data, propose rotational crop tolerances for crops that are specified on product labels. If the registrant elects the latter, extensive field rotational crop studies will be required; these field trial data will be considered confirmatory (OPPTS Guideline 860.1850, 850.1900).

Occupational Exposure Data Requirements

- **Guideline 231 - Estimation of Dermal Exposure at Outdoor Sites.** Studies are required for handlers in double-layer body protection and chemical-resistant gloves and, additional studies are required for handlers using engineering controls, as follows:

    - mixing and loading with granulars and emulsifiable concentrates;
    - broadcast and banding application of granulars;
    - groundboom application of emulsifiable concentrates; and
    - soil injection application.

- **Guideline 232 - Estimation of Inhalation Exposure at Outdoor Sites.** Studies are required for handlers wearing respirators and additional studies are required for handlers using engineering controls, as follows:

- mixing and loading with granulars and emulsifiable concentrates;
- broadcast and banding application of granulars;
- groundboom application of emulsifiable concentrates, and
- soil injection application.

❖ **Guideline 132-1(a) - Foliar Dislodgeable Residue Dissipation**. Postapplication exposure data are required to support the reregistration of fenamiphos (golf course turf). Previously, the Agency granted a waiver for both the DFR data requirement and the 48-hour reentry for the golf course use. However, in light of FQPA, the data waiver is no longer applicable. The registrant needs to provide a turf dislodgeable foliar residue study to refine postapplication exposure estimates.

❖ **Guideline 132-1(b) - Soil Residue Dissipation**. Postapplication exposure data are required to support the reregistration of fenamiphos.

❖ **Guideline 133-3 - Dermal Exposure**. Postapplication exposure data are required to support the reregistration of fenamiphos.

❖ **Guideline133-4 - Inhalation Exposure**. Inhalation exposure data are required for the uses that may involve human contact with treated soil. These include: pre-transplant strawberries and asparagus, ornamental nonflowering plants, ornamental herbaceous plants, sod farm turf, ornamental woody shrubs and vines, and all nursery stock. Data are required using both the EC and granular formulations.

❖ The Agency requires data and/or further clarification of the use patterns involving workers handling or working with or in the treated soil which may result in postapplication exposure. These uses are on strawberries, asparagus, ornamental nonflowering plants, ornamental herbaceous plants, sod farm turf, ornamental woody shrubs and vines, and all nursery stock. For these sites the 48-hour REI will be required, until receipt and evaluation of the additional data. The Agency requires confirmation that the golf course use does not result in postapplication exposure as a result of handling treated grass clippings.

II. Use Profile

Fenamiphos (Ethyl 3-methyl-4-(methylthio)phenyl-1-(methylethyl) phosphoramidate) is an organophosphate insecticide/nematicide. End-use products include granulars and emulsifiable concentrates. The granular formulations contain 10 and 15 percent active ingredient, respectively. The emulsifiable concentrate formulation contains 35 percent active ingredient.

Fenamiphos is labeled for use on terrestrial food, nonfood, and food and feed crops. Use sites are quite varied and include: low, mid-height, and orchard type agricultural crops; turf uses; and ornamental uses. More specifically, agricultural use sites include: low crops (*i.e.*, asparagus, beets, Brussels sprouts, cabbage, Chinese cabbage, eggplant, garlic, okra, unspecified peanuts, peppers, pineapples, and strawberries); mid-level crops (*i.e.*, cotton, grapes, kiwi, black and red raspberry, and tobacco); and orchard type crops (*i.e.*, apple, cherry, citrus, unspecified deciduous fruit trees, nectarine, unspecified orchards, peaches, and tree nuts). Turf use sites include commercial and industrial lawns; ornamental lawns and turf; sod farms and golf courses. Additionally, ornamental uses include: ornamental and/or shade trees; ornamental herbaceous plants; ornamental nonflowering plants; and ornamental woody shrubs and vines. All uses appear to be outdoors except for some of the ornamental uses which may be inside of greenhouses. Fenamiphos controls several varieties of nematodes, thrips, beetles, aphids, and root borers. There are no residential turf uses permitted for fenamiphos at this time for any label or end-use-product; however, there is potential for nonoccupational postapplication exposure from application of fenamiphos to golf course turf.

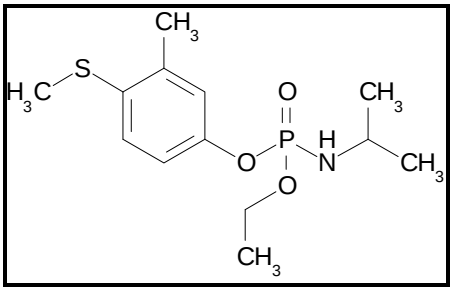
Applications can be made using ground equipment or chemigation. Additionally, a majority of the available labels preclude the use of any knapsack/backpack type equipment. Application types include: chemigation (*i.e.*, low-pressure irrigation and solid-set irrigation); soil band treatments (*i.e.*, granulars and emulsifiable concentrates); broadcast treatments (*i.e.*, granulars and emulsifiable concentrates); in-furrow treatments; soil injection; and spray/foliar treatments. A majority of the labeled uses require that the applications are soil incorporated and/or watered-in via irrigation or natural rainfall. Additionally, the timing for a majority of applications is at or near planting or the dormant stage for most of the labeled targets (*i.e.*, timing for most application scenarios: posttransplant, postharvest, preemergence, pretransplant, preplant, or at planting). Chemigation application rates (*i.e.*, EC formulation only) range up to 4.5 lb ai/acre for typical low-pressure irrigation and up to 12 lb ai/acre for solid-set irrigation techniques. Rates for ground-based applications of the emulsifiable concentrate formulations range up to: 20 lb ai/acre for broadcast applications; 10 lb ai/acre for soil banding and spray applications; 3 lb ai/acre for soil injection applications and 2.175 lb ai/acre for in-furrow treatments. Rates for the ground-based application of the granular formulations range up to: 10.05 lb ai/acre for banding (*i.e.*, other banding rates were specified based on the row length -- maximum reported

was 0.1725 lb ai/1000 linear feet); and 10 lb ai/acre for broadcast and in-furrow applications.

III. Physical and Chemical Properties

A. Description of Chemical

Fenamiphos (O-ethyl-O-(3-methyl-4-methylthiophenyl)-isopropylphosphoramidate) is a systemic nematicide/insecticide used for the control of nematodes and thrips on terrestrial food crops and nonfood sites.



Empirical Formula: $C_{13}H_{22}NO_3PS$
Molecular Weight: 303.4 g/mole
CAS Registry No.: 22224-92-6
Shaughnessy No.: 100601

B. Identification of Active Ingredient

Technical fenamiphos is an off-white to tan waxy solid with a melting point of 49°C and a vapor pressure of 4.7×10^{-5} mm Hg at 20°C. Fenamiphos is soluble in dichloromethane, 2-propanol, and toluene, only slightly soluble in n-hexane, and insoluble in water.

C. Manufacturing-Use Products

A search of the OPP Reference Files System (REFS) conducted 5/26/93 identified two fenamiphos manufacturing-use products (MPs), an 85% technical (T; EPA Reg. No. 3125-269) and a 72.3% formulation intermediate (FI; EPA Reg. No. 3125-333), both registered to Bayer, Inc. (formerly Mobay Corp.). We note that although REFS lists the label claim as 85% for the Bayer technical (EPA Reg. No. 3125-269), the Registration Standard (1987) refers to the product as a 90% T, and the Registration Standard Update (2/92) refers to the product by the reported nominal concentration (92.5%). The technical product will be referenced throughout this document by the label claim listed in REFS (85% T). Only the two Bayer, Inc. MPs are subject to a reregistration eligibility decision.

D. Product Chemistry Data Requirements

The registrant must submit: 830.1600 – Description of materials used to produce the product; 830.1620 --Description of production process; 830.1670 – Discussion of formation of impurities; 830.1700 -- Preliminary analysis; 830.1750 -- Certification of ingredient limits; 830.1800 -- Analytical methods to verify the certified limits for the 85% T (EPA Reg. No. 3125-269); 830.1550 – Product identity and disclosure of ingredients for the 72.3% FI (EPA Reg. No. 3125-33);and either certify that the suppliers of starting materials and the manufacturing process for the fenamiphos products have not changed since the last comprehensive product chemistry review or submits a complete updated product chemistry data package. These data are considered confirmatory.

Data pertaining to the nitrosamine content of some fenamiphos products is outstanding, but is not expected to be of dietary concern since nitrosamines have not been detected in previously submitted studies for some products.

IV. Human Health Assessment

A. Hazard Assessment

The toxicology database for fenamiphos is complete. The acute toxicity profile is presented in Table 1. Fenamiphos is placed in Toxicity Category I for acute oral and dermal toxicity and in Toxicity Category II for acute inhalation toxicity. Fenamiphos is mildly irritating to the eyes (Toxicity Category III), non-irritating to the skin (Toxicity Category IV), and is not a dermal sensitizer. Fenamiphos did not induce Organophosphate Induced Delayed Neurotoxicity (OPIDN) in hens. No treatment-related pathological lesions were seen in the central or peripheral nervous system of rats following a single gavage dose or repeated dietary administration. The principal toxicological effects in rats and dogs following subchronic and chronic oral (dietary) exposure was inhibition of plasma, red blood cell and/or brain cholinesterase activity. Repeated dermal applications to rabbits for 21-days resulted in inhibition of plasma, erythrocyte and brain cholinesterase activity. There was no evidence of carcinogenicity in mice and rats when tested at doses that were judged to be adequate to assess carcinogenicity. Fenamiphos was nonmutagenic both *in vivo* and *in vitro*. Fenamiphos is classified as a Group E chemical; not classifiable as to human carcinogenicity based on the lack of carcinogenic potential which is supported by the lack of mutagenic activity. There was no evidence of increased susceptibility of rat or rabbit fetuses following *in utero* exposure in prenatal developmental toxicity studies, no offspring toxicity was seen at the highest dose tested (HDT) in the two-generation reproduction toxicity study, and there was no evidence of abnormalities in the development of the fetal nervous system in these studies.

The reports of the various HED Science Assessment Review Committees are presented in Attachments 1 through 5.

Table 1. Acute Toxicity Technical Fenamiphos

Test	Result	Category
Acute Oral LD_{50} (rat)	2.7 mg/kg M[2] 3.0 mg/kg F[3]	I
Acute Dermal LD_{50} (rabbit)	225 mg/kg M 178.8 mg/kg F	I
Acute Inhalation LC_{50} (rat)	> 0.1 mg/L (nominal but 0.02 μL analytical)	II
Eye Irritation (rabbit)	mild irritation	III
Dermal Irritation (rabbit)	not irritating	IV
Skin Sensitization (guinea pig)	negative	-

[1]Based on the technical grade fenamiphos.
[2]M = Male; [3]F = Female

1. Acute Toxicity

The LD_{50} for 88% fenamiphos from an acute oral Sprague-Dawley rat study was 2.7 mg/kg and 3.0 mg/kg in males and females, respectively (Guideline 81-1; MRID 00033831). Similar oral LD_{50} values were obtained with fenamiphos in mice, rabbits, cats, dogs, and hens. In contrast, oral LD_{50} values for most metabolites of fenamiphos exceeded 1000 mg/kg (HED Document No. 1310).

The LD_{50} for technical fenamiphos from an acute dermal study was 225 mg/kg in male and 178.8 mg/kg in female New Zealand white rabbits, respectively (Guideline 81-2; MRID 00037962). The LC_{50} for a rat inhalation study with 89.9% fenamiphos in THO/W74 rats of both sexes was > 0.1 mg/L (based on the nominal concentration but 0.02 μg/L based on the analytical concentration) for a four-hour exposure (Guideline 81-3; MRID 00154492). Ocular application of fenamiphos to rabbits produced mild chemosis and iritis with category III toxicity (Guideline 81-4; MRID 00082111). A primary dermal irritation study indicated that fenamiphos was not a skin irritant (Guideline 81-5; MRID 00082111). No dermal sensitization occurred with 90.2% fenamiphos in Hartley guinea pigs (Guideline 81-6; MRID 00148464). Fenamiphos was not neurotoxic when administered in a single oral dose to white leghorn hens in an acute delayed neurotoxicity study (Guideline 81-7; MRID 00057606).

2. Subchronic Toxicity

Subchronic studies were conducted in two strains of rats following dietary exposures. In one study Wistar rats received diets containing fenamiphos at doses of 0, 4, 8, 16, or 32 ppm (equivalent to 0, 0.2, 0.4, 0.8 or 1.6 mg/kg/day, respectively) for 13 weeks. The NOAEL was 0.2 mg/kg/day based on plasma and red cell cholinesterase inhibition at 0.4 mg/kg/day (LOAEL) (Guideline 82-1; MRID 00117403). In the other study, Fisher 344 rats were fed fenamiphos in the diet at doses of 0, 0.36, 0.6, or 1.0 ppm (0, 0.018, 0.03, or 0.05 mg/kg/day, respectively) for 13 weeks. The NOAEL was 0.05 mg/kg/day, HDT) [Guideline 82-1; MRID 00133475 (HED Document No. 3606)].

Two subchronic studies were available following dietary exposures to beagle dogs. In one study, dogs received fenamiphos in the diet at doses of 0, 1, 2, or 5 ppm (0, .025, 0.05, or 0.125 mg/kg/day, respectively) for 90-days. The NOAEL was 0.025 mg/kg/day and the LOAEL was 0.05 mg/kg/day, based on dose-related plasma cholinesterase inhibition. Erythrocyte cholinesterase inhibition and growth depression occurred at the HDT (0.125 mg/kg/day) (Guideline 82-1; MRID 00119238, 0119957 [HED Document No. 1310]). In a second study, the doses tested were 0, 0.6, 1.0, or 1.7 ppm (0, 0.015, 0.025, 0.042 mg/kg/day, respectively) for 90-days. The NOAEL was 0.025 mg/kg and the LOAEL was 0.042 mg/kg/day based on depressed plasma cholinesterase activity (Guideline 82-1; MRID 0154493 [HED Document No. 4602]).

In a 21-day dermal toxicity study, groups of New Zealand white rabbits (2/sex/dose) received repeated dermal applications of technical fenamiphos in an aqueous formulation (89.8%) at doses of 0, 0.5, 2.5, and 10 mg/kg/day, 6 hours/day, 5 days/week for three weeks. Blood cholinesterase was determined on days 0, 10, and 15 of the study. At 10 mg/kg, plasma cholinesterase was decreased in male and female rabbits on day 10 by 42% and 40%, respectively; blood cholinesterase was decreased in male and female rabbits on day 10 by 23% and 41%, respectively; brain cholinesterase was decreased in male and female rabbits on day 10 by 11% and 23%, respectively (non-abraded skin for all effects). At 2.5 mg/kg/day, plasma cholinesterase in female rabbits was decreased by 30% on day 10; brain cholinesterase was decreased in female rabbits on day 15 by 11%. No decreases in cholinesterase were noted in male rabbits at 2.5 mg/kg/day (non-abraded skin for all effects). The NOAEL was determined to be 2.5 mg/kg/day based on the marginal effects observed at this dose. Inhibition of plasma and brain cholinesterase in female rabbits at 10 mg/kg/day on day 10. At the 10 mg/kg/day dose level on day 10, inhibition of plasma, blood, and brain

cholinesterase was observed in both male and female rabbits, whereas at the 2.5 mg/kg/day dose on day 10, only inhibition of plasma cholinesterase (30% decrease) in females was observed. At the 2.5 mg/kg/day dose, the effect on brain cholinesterase (11% decrease) in females could have been the result of unusually high control values. In addition, variability in the response of plasma and red cell cholinesterase was observed at 2.5 mg/kg/day. Therefore, the 2.5 mg/kg/day dose was considered a NOAEL and appropriate for risk assessments (MRID 00154497; HED Document Nos. 4531, 5722).

In a 21-day inhalation study, Wistar rats (10/sex/concentration) were exposed "nose only" to concentrations of fenamiphos at 0, 0.03, 0.25 or 3.5 μg/L for 6-hours/day, 5 days/week over a three-week period. Ninety eight percent of the particles were 3μ or less. The NOAEL was 0.25 μg/L and the LOAEL was 3.5 μg/L based on inhibition of plasma cholinesterase activity in males (42-47%) and females (72-78%) and erythrocyte activity in females (15-19%) (Guideline 82-4; MRID 40774809 [HED Document No. 11035]).

3. Chronic Toxicity

In a chronic toxicity study, beagle dogs (4/sex/dose) were fed diets containing fenamiphos (technical) at 0, 1.0, 3.0, or 12.0 ppm (0, 0.03, 0.08, or 0.3 mg/kg/day respectively) for 12 months. Based on plasma cholinesterase inhibition of 25-32% in males and 20-26% in females, the LOAEL was 0.03 mg/kg/day, the lowest dose tested; a NOAEL was not established for this effect. For systemic toxicity, the NOAEL was 0.08 mg/kg/day and the LOAEL was 0.3 mg/kg/day based on anemia observed in males (MRID 42183601).

In a follow-up study, to establish a NOAEL for plasma cholinesterase activity, beagle dogs (4/sex/dose) received fenamiphos (technical) in the diet at 0.5 ppm (0.0108 and 0.0115 mg/kg/day, in males and females, respectively) for 180 days. No statistically-significant inhibition of plasma or erythrocyte activity was seen at this dose (MRID 42684801)

The combination of these two studies yielded a NOAEL of 0.01 mg/kg/day and a LOAEL of 0.03 mg/kg/day for inhibition cholinesterase activity (Guideline 83-1(a); MRID 42183601; 42684801 [HED Document No. 10241]).

In a combined chronic toxicity/carcinogenicity study Fischer 344 rats (60/sex/dose) were fed diets containing fenamiphos at 0, 2, 10, or 50

ppm (equivalent to 0, 0.098, 0.46, or 2.45 mg/kg/day for males and 0, 0.12, 0.6, or 3.36 mg/kg/day for females, respectively) for 104 weeks. Inhibition of plasma and red cell cholinesterase activity was seen at all dose levels including the lowest dose (2 ppm); a NOAEL was not established for this effect. For systemic toxicity the NOAEL was 10 ppm (0.46 mg/kg/day in males and 0.6 mg/kg/day in females)(and the LOAEL was 50 ppm (2.45 mg/kg/day in males and 3.36 mg/kg/day in females) based upon reduction in body weight gain and food consumption, as well as decreased liver and increased lung weights. This was accompanied by granulomatous inflammation of the lungs in both sexes at the high dose level. There was no evidence of carcinogenicity in either sex of rats. (Guidelines 83-1, 83-2; 83-5 MRID 00161361, 40329601 [HED Document Nos. 3331, 3606, 5682, 5722]).

4. Carcinogenicity

The carcinogenic potential of fenamiphos has been evaluated following long-term exposures to mice and two strains of rats.

In a carcinogenicity study, CD albino mice (50/sex/dose) received diets containing fenamiphos at doses of 0, 2, 10, or 50 ppm (0, 0.2, 1.0, or 5.0 mg/kg/day, respectively). Body weight was reduced at the highest dose level. There was no evidence of carcinogenicity in either sex (Guidelines 83-1(b), 83-2(b); MRID 00098614; HED Document Nos. 2241, 5722).

In Fischer rats, (as discussed above in chronic toxicity), no evidence of carcinogenicity was seen in males or females following dietary exposures at 0, 2, 10, or 50 ppm for 104 weeks (Guidelines 83-1, 83-2; MRID 00161361, 40329601; HED Document Nos. 3331, 3606, 5682, 5722).

In Wistar rats, dietary administration of fenamiphos at 0, 3, 10, or 30 ppm (0.15, 0.5, or 1.5 mg/kg/day) produced no evidence of carcinogenicity in either sex (Guideline 83-2(a); MRID 00038490; HED Document No. 1314).

On May 20, 1993, the HED RfD Peer Review Committee determined that the high-dose levels tested in rats and mice were adequate to assess the carcinogenic potential of fenamiphos.

5. Developmental Toxicity

In a developmental toxicity study with CD rats, pregnant animals were given oral doses of Fenamiphos at 0, 0.25, 0.85, or 3.0 mg/kg/day during gestation days six through 15. For maternal toxicity, the NOAEL was 0.85 mg/kg/day and the LOAEL was 3.0 mg/kg/day based on increased mortality, reduction in body weight gain and food consumption, cholinergic signs and plasma and erythrocyte cholinesterase activity. For developmental toxicity, the NOAEL was 3.0 mg/kg/day (HDT); a LOAEL was not established (Guideline 83-3(a); MRID 41225401; HED Document No. 7669).

In a developmental toxicity study, artificially pregnant Chinchilla rabbits received oral doses of fenamiphos at 0, 0.1, 0.5 or 2.5 mg/kg/day during gestation days six through 18. For maternal toxicity, the NOAEL was 0.5 mg/kg/day and the LOAEL was 2.5 mg/kg/day based on cholinergic signs. For developmental toxicity, the NOAEL was 2.5 mg/kg/day (HDT); a LOAEL was not established. The HED RfD Committee considered the skeletal anomalies at 2.5 mg/kg/day to be an isolated incident and not treatment-related (Guideline 83-3(b); MRID 40347602; HED Document No. 6666).

6. Reproductive Toxicity

In a two-generation reproduction study, when administered in the diet at 0, 2.5, 10 or 30 ppm (0, 0.17, 0.64 or 2.8 mg/kg/day for males and 0, 0.2, 0.73, or 3.2 mg/kg/day for females) to Sprague-Dawley rats, no increased sensitivity to pups over the adults was seen. For parental systemic toxicity, the NOAEL was 0.17 mg/kg/day for males and <0.2 mg/kg/day for females. The LOAEL was 0.64 mg/kg/day for males and 0.2 mg/kg/day for females. In both sexes, the LOAELs were based on inhibition of plasma and RBC cholinesterase activity. For systemic (non-cholinergic) toxicity to the offspring and for reproductive toxicity, the NOAELs were 3.2 mg/kg/day (HDT); LOAELs were not established (Guideline 83-4; MRID 41908901, 42491701; HED Document No. 9473).

In a three-generation reproduction study, when administered in the diet at 0, 3, 10 or 30 ppm (0, 0.15, 0.5, or 1.5 mg/kg/day, respectively) to rats, no increased sensitivity to pups over the adults was seen. For parental toxicity, the NOAEL was 0.5 mg/kg/day and the LOAEL was 1.5 mg/kg/day based on reduced body weight gain in F2b males. For reproductive and offspring toxicity, the NOAEL was 1.5 mg/kg/day (HDT); a LOAEL was not established (Guideline 83-4; MRID 41908901, 42491701;HED Document No. 9473).

7. Neurotoxicity

In an acute neurotoxicity screening battery in rats, fasted (overnight) male and female Wistar rats (18/sex/dose) were given a single oral (gavage) dose of fenamiphos at 0, 0.4, 1.6, or 2.4 mg/kg (analytically confirmed doses: 0, 0.37, 1.52, and 2.31 mg/kg). The main study animals (12 rats/sex/dose, except the high-dose male group which contained 15 rats) were used for a routine neurotoxicity screening battery with behavioral testing at the peak time of effect (25 min postdosing) and at days seven and 14 postdosing; neuropathological examination was carried out at terminal sacrifice (day 14). Plasma, RBC and brain cholinesterase activities were measured in 6 rats/sex/dose) at approximately 50 minutes postdosing. No treatment-related changes were noted in mean body weights, absolute and relative brain weights and the incidences of gross and neurohistopathological lesions. At the high-dose, fenamiphos toxicity was observed within 21 to 31 min postdosing (lethality 7/15 males, 1/12 females), with clinical signs of cholinesterase inhibition persisting to approximately 2 hr 45 min postdosing. At 4 to 8 hr postdosing, all treatment-related clinical signs were absent. Although plasma and RBC ChE activities were markedly and rapidly (50 min postdosing) inhibited, brain ChE was unaffected. The following treatment-related effects were observed: at 2.31 mg/kg lethality in males and females, muscle fasciculations, gait incoordination, nasal and oral staining, constricted pupils, salivation, lacrimation (females only), and piloerection, statistically-significant decreases in plasma and RBC ChE activities, and decreased motor and locomotor activities in males; at 1.52 mg/kg muscle fasciculations in males, statistically-significant decreases in plasma and RBC ChE activities and at 0.37 mg/kg statistically-significant decreases in plasma ChE in females and RBC ChE in males with a nonsignificant decrease in plasma ChE in males. Based on the results of this study (inhibition of plasma and RBC), the LOAEL was established at 0.37 mg/kg; the NOAEL was not established (Guideline 81-8; MRID 44041501).

In a subchronic neurotoxicity screening battery male and female

Wistar rats (12/sex/dose) were fed diets containing fenamiphos at 0 (basal diet), 1, 10, or 50 ppm (equivalent to 0, 0.06, 0.61, or 3.13 mg/kg/day, males; 0, 0.08, 0.8, 3.98 mg/kg/day, females) for at least 13 weeks. Routine neurotoxicity screening battery consisting of Functional Observational Battery (FOB) and motor activity measurements were performed at prestudy and after 4, 8 and 13 weeks of treatment. Gross pathology (all animals) and neuropathological (6/sex/dose) examinations were carried out at terminal sacrifice. Plasma and RBC cholinesterase activities were measured in 6/sex/dose at Week 4; plasma, RBC and brain cholinesterase activities were measured on animals not selected for neuropathological examination at Week 15. No treatment-related changes were noted in mean body weights or absolute and relative brain weights. The incidences of gross and neuropathological finding of treated animals were comparable to controls. Dose-related increases in motor and locomotor activity were observed in females at Week 13. This effect was judged to be equivocal since a similar "dose-related" increase was observed during the pre-study evaluations. Additionally, none of the motor or locomotor activities achieved statistical significance. No treatment-related effects were observed in animals dosed at 1 ppm. At 10 ppm, decreases in plasma ChE activity at Week 4 and Week 15 and RBC ChE activity at Week 4 and Week 15 were observed. At 50 ppm, an increased incidence of muscle fasciculations in all females during weeks one to three was noted. At Week 4 and Week 15, statistically-significant decreases in plasma ChE activity and RBC ChE was observed. Brain ChE was slightly (but statistically-significant) decreased (-12%) at Week 15 in females. Based on the results of this study (inhibition of plasma and RBC ChE), the LOAEL was established at 10 ppm (0.61 mg/kg/day, males; 0.8 mg/kg/day, females); the NOAEL was established at 1 ppm (0.06 mg/kg/day, males; 0.08 mg/kg/day, females) (Guideline 82-5; MRID 44041502 and 44051401;HED Document No. 012019).

8. Mutagenicity

Fenamiphos was not mutagenic in studies designed to detect gene mutations. These were the CHO/HGPRT assay *in vitro* (Guideline 84-2(a); MRID 00159127) and the Ames reversion assay with *S. typhimurium* (Guideline 84-2(a); MRID 40319001). Structural chromosomal aberrations were not found in the dominant lethal test in mice (Guideline 84-2(b); MRID 00086981). The *B. subtilis* rec assay (MRID 00161367; HED Document No. 5682) and the unscheduled DNA synthesis assay in primary rat hepatocytes were negative (Guideline 84-4; HED Document No. 5682 and MRID 40649101).

9. Metabolism

Metabolism studies in the rat indicated no major differences between oral and intravenously (i.v.) administered fenamiphos (Guideline 85-1; MRID 's 41194901 and 41194902). Orally administered compound was rapidly absorbed, and compounds given by both routes were immediately metabolized and excreted. The major metabolites were sulfoxides and sulfates, nine of which were found in urine, with only a single major metabolite in feces. Within 48 hours after oral or i.v. dosing with radiolabelled compound, 93 to 100% of the administered dose was found in urine, 1.5 to 3.8% in feces, and less than 0.1% in CO_2. Tissue levels of radioactivity were highest at 48 hours in liver, kidneys and skin. Based on the data, a metabolic pathway was proposed for fenamiphos.

B. Dose Response Assessment

1. Special Sensitivity to Infants and Children

On August 8, 1998, the HED FQPA Safety Factor Committee evaluated both the hazard and exposure data and recommended that the 10X FQPA safety factor for fenamiphos could be removed based on the following factors:

(a) In prenatal developmental toxicity studies following *in utero* exposure in rats and rabbits, there was no evidence of developmental effects being produced in fetuses at lower doses as compared to maternal animals, nor was there evidence of an increase in severity of effects at or below maternally toxic doses.

(b) In the pre/post-natal two-generation reproduction study in rats, there was no evidence of enhanced susceptibility in pup when compared to adults (*i.e.*, effects noted in offspring occurred at maternally toxic doses or higher).

(c) There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post-natal studies.

(d) There is no concern for positive neurological effects from the available neurotoxicity studies or for histopathology in the central nervous system from the other toxicological studies (*e.g.*, subchronic rat, chronic dog, chronic mouse and rat) therefore a developmental neurotoxicity study is not required.

(e) The toxicology database is complete and there are no data gaps according to the Subdivision F Guideline requirements.

(f) Adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess dietary (food and water) exposure and to provide a screening level drinking water exposure assessment.

2. Toxicology Endpoint Selection

Presented below are the toxicology endpoints selected for acute and chronic dietary as well as occupational and nonoccupational exposure risk assessments by the Hazard Identification Assessment Review Committee (HIARC). The endpoints are summarized at the end of this section, in Table 2.

a. Acute Dietary (Acute Reference Dose)

In an acute neurotoxicity screening battery in rats, fasted (overnight) male and female Wistar rats (18/sex/dose) were given a single oral (gavage) dose of fenamiphos at 0, 0.4, 1.6, or 2.4 mg/kg (analytically confirmed doses: 0, 0.37, 1.52, and 2.31 mg/kg). The main study animals (12 rats/sex/dose, except the high-dose male group which contained 15 rats) were used for a routine neurotoxicity screening battery with behavioral testing at the peak time of effect (25 min postdosing) and at days seven and 14 postdosing; neuropathological examination was carried out at terminal sacrifice (day 14).

Plasma, RBC and brain cholinesterase activities were measured in 6 rats/sex/dose at approximately 50 min postdosing. No treatment-related changes were noted in mean body weights, absolute and relative brain weights and the incidences of gross and neurohistopathological lesions. At the high-dose, fenamiphos toxicity was observed within 21 to 31 min postdosing (lethality 7/15 males, 1/12 females), with clinical signs of cholinesterase inhibition persisting to approximately 2 hr 45 min postdosing. At 4 to 8 hr postdosing, all treatment-related clinical signs were absent. Although plasma and RBC ChE activities were markedly and rapidly (50 min postdosing) inhibited, brain ChE was unaffected. The following treatment-related effects were observed: at 2.31 mg/kg lethality in males and females, muscle fasciculations, gait incoordination, nasal and oral staining, constricted pupils, salivation, lacrimation (females only), and piloerection, statistically-significant decreases in plasma and RBC ChE activities, and decreased motor and locomotor activities in males; at 1.52 mg/kg muscle fasciculations in males, statistically-significant decreases in plasma and RBC ChE activities; and at 0.37 mg/kg statistically-significant decreases in plasma ChE in females and RBC ChE in males with a nonsignificant decrease in plasma ChE in males. Based on the results of this study (inhibition of plasma and RBC), the LOAEL was established at 0.37 mg/kg; a NOAEL was not established (MRID 44041501).

An acute Reference Dose of 0.0012 mg/kg was derived based on the LOAEL of 0.37 mg/kg and an UF of 300. The UF of 300 includes the conventional UF of 100 (10X for interspecies extrapolation and 10X for intraspecies variation) and an additional UF of three for the use of the LOAEL (*i.e*., lack of a NOAEL in the critical study).

$$\textbf{Acute PAD} = \frac{\text{0.37 mg/kg/day (LOAEL)}}{\text{300 (UF)}} = \textbf{0.0012 (mg/kg/day)}$$

As per current Office of Pesticide Programs (OPP) policy, an RfD modified by an FQPA safety factor is referred to as an Acute Population Adjusted Dose (aPAD). Because the FQPA safety factor was removed for fenamiphos, the acute PAD is equal to the acute RfD.

b. Chronic Dietary (Chronic Reference Dose)

In a chronic toxicity study, beagle dogs (4/sex/dose) were fed diets containing fenamiphos (technical) at 0, 1.0, 3.0 or 12.0 ppm (0, 0.03, 0.08 or 0.3 mg/kg/day respectively) for 12 months. Based on plasma cholinesterase inhibition of 25-32% in males and 20-26% in females, the LOAEL was 0.03 mg/kg/day, the lowest dose tested; a NOAEL was not established for this effects. For systemic toxicity, the NOAEL was 0.08 mg/kg/day and the LOAEL was 0.3 mg/kg/day based on anemia observed in males (MRID 42183601).

In a follow-up study, to establish a NOAEL for plasma cholinesterase activity, beagle dogs (4/sex/dose) received fenamiphos (technical) in the diet at 0.5 ppm (0.0108 and 0.0115 mg/kg/day, in males and females, respectively) for 180 days. No statistically-significant inhibition of plasma or erythrocyte activity was seen at this dose (MRID 42684801).

The combination of these two studies yielded a NOAEL of 0.01 mg/kg/day and a LOAEL of 0.03 mg/kg/day for inhibition cholinesterase activity.

A chronic Reference Dose of 0.0001 mg/kg/day was derived based on the NOAEL of 0.01 mg/kg/day in the dogs and an UF of 100 which included a 10X for interspecies extrapolation and 10X for intraspecies variation.

Chronic PAD = $\frac{0.10 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}}$ = **0.0001 mg/kg/day**

As per current OPP policy, an RfD modified by an FQPA safety factor is referred to as an Chronic Population Adjusted Dose (cPAD). Because the FQPA safety factor was removed for fenamiphos, the chronic PAD is equal to the acute RfD.

c. Carcinogenicity Classification

Based on the lack of evidence of carcinogenicity in mice or rats at doses that were judged to be adequate to assess the carcinogenic potential of the organophosphate, fenamiphos is classified as a Group E chemical (evidence of non-carcinogenicity in for humans).

d. Dermal Absorption Factor

A dermal absorption factor is not required since a NOAEL from a dermal toxicity study was selected for short-and intermediate-term risk assessments. Fenamiphos is not expected to be used continuously for greater than or equal to six months for the uses subject to reregistration. Consequently, a long-term dermal exposure and risk assessment is not a required at this time.

e. Short- and Intermediate-Term Dermal

In a 21-day dermal toxicity study, groups of New Zealand white rabbits (2/sex/dose) received repeated dermal applications of technical fenamiphos in an aqueous formulation (89.8%) at doses of 0, 0.5, 2.5, and 10 mg/kg/day, 6 hours/day, 5 days/week for three weeks. Blood cholinesterase was determined on days 0, 10, and 15 of the study. At 10 mg/kg, plasma cholinesterase was decreased in male and female rabbits on day 10 by 42% and 40%, respectively; blood cholinesterase was decreased in male and female rabbits on day 10 by 23% and 41%, respectively; brain cholinesterase was decreased in male and female rabbits on day 10 by 11% and 23%, respectively (non-abraded skin for all effects).

At 2.5 mg/kg/day, plasma cholinesterase in female rabbits was decreased by 30% on day 10; brain cholinesterase was decreased in female rabbits on day 15 by 11%. No decreases in cholinesterase were noted in male rabbits at 2.5 mg/kg/day (non-abraded skin for all effects). The NOAEL was determined to be 2.5 mg/kg/day based on the marginal effects observed at this dose. Inhibition of plasma and brain cholinesterase in female rabbits at 10 mg/kg/day on day 10 was observed. At the 10 mg/kg/day dose level on day 10, inhibition of plasma, blood, and brain cholinesterase was observed in both male and female rats, whereas at the 2.5 mg/kg/day dose on day 10, only inhibition of plasma cholinesterase (30% decrease) in females was observed. At the 2.5 mg/kg/day dose, the effect on brain cholinesterase (11% decrease) in females could have been the result of unusually high control values. In addition, variability in the response of plasma and red cell cholinesterase was observed at 2.5 mg/kg/day. Therefore, the 2.5 mg/kg/day dose was considered a NOAEL and appropriate for risk assessments (MRID 0154497).

The dermal NOAEL of 2.5 mg/kg/day was selected for short- and intermediate-term dermal exposure risk assessments by

the Toxicology Endpoint Selection Committee. This dose was confirmed later by the HIARC at their meetings on 9/18/97 and 5/12/98. A MOE greater than 100 does not exceed the Agency's level of concern for these risk assessments.

f. Short- and Intermediate-Term Inhalation

In a 21-day inhalation study, Wister rats (10/sex/concentration) were exposed "nose only" to concentrations of fenamiphos at 0, 0.03, 0.25 or 3.5 μg/L for 6 hours/day, 5 days/week over a three-week period. The NOAEL was 0.25 μg/L and the LOAEL was 3.5 μg/L based on inhibition of plasma cholinesterase activity in males (42-47%) and females (72-78%) and erythrocyte activity in females (15-19%) (MRID 40774809).

The NOAEL of 0.25 μg/L (0.061 mg/kg) selected for short- and intermediate-term inhalation exposure risk assessments were confirmed by the HIARC. A MOE greater than 100 does not exceed the Agency's level of concern for these risk assessments.

g. Long-Term Dermal and Inhalation

No long term dermal or inhalation exposure is expected, because the use pattern for this chemical indicates that it is not expected to be used continuously for greater than or equal to six months for the uses currently subjected to reregistration.

Table 2. Summary of Toxicological Endpoints for Fenamiphos

Exposure Duration	Exposure Route	Endpoint
Acute	Dietary	LOAEL of 0.37 mg/kg/day UF= 300 FQPA = 1
	Acute RfD = 0.0012 mg/kg aPAD = 0.0012 mg/kg	
Chronic (non-cancer)	Dietary	NOAEL of 0.01 mg/kg/day UF= 100 FQPA = 1
	Chronic RfD = 0.0001 mg/kg/day cPAD = 0.0001 mg/kg/day	
Chronic (cancer)	Dietary/Dermal/ Inhalation	None - classified as a Group E
Short-Term and Intermediate-Term Occupational	Dermal	Dermal NOAEL of 2.5 mg/kg/day MOE of 100 is required
Short-Term and Intermediate-Term Occupational	Inhalation	Inhalation NOAEL of 0.25 µg/L MOE of 100 is required

3. Dietary Exposure and Risk Characterization

a. Dietary Exposure - Food Sources

There are two end-use products (EPs) of fenamiphos presently registered to Bayer, Inc. (formerly Mobay Corporation) which may be used on food/feed crops grown in the U.S.; these EPs include a 15% G (Nemacur®15%; EPA Reg. No. 3125-236) and a 3 lb/gal EC (Nemacur®3; EPA Reg. No. 3125-283) formulation. The registrant has recently submitted copies of 10% G labels with English translations from Costa Rica, Ecuador, Guatemala, and Philippines which use fenamiphos on bananas that are exported to the U.S. market.

A comprehensive summary of the registered food/feed use patterns of fenamiphos, based on these product labels, has been presented in the Chemistry Chapter of the HED Reregistration Eligibility Decision (RED) Document. The conclusions regarding the reregistration eligibility of fenamiphos for the crops listed in this chapter are based on the use patterns registered by the basic producer, Bayer, Inc. and summarized in the tolerance

reassessment summary of this document. All end-use product labels (*e.g.*, MAI labels, SLNs, and products subject to the generic data exemption) must be amended such that they are consistent with the basic producer labels.(Guideline 860.1200).

(i). Nature of the Residue Plants and Animals

The qualitative nature of the residue in plants is adequately understood. Studies with a variety of plants including beans, cabbage, carrots, mustard, oats, peanuts, pineapples, potatoes, soybeans, sugar beets, tobacco, tomatoes, and wheat indicate that fenamiphos is absorbed from soils, foliage, and fruits and translocated throughout the plant. Metabolism involves the oxidation of fenamiphos to fenamiphos sulfoxide and/or fenamiphos sulfone, subsequent hydrolysis to fenamiphos sulfoxide phenol and fenamiphos sulfonephenol, and the formation of the glucoside or other conjugates. The terminal residues of concern are fenamiphos, fenamiphos sulfoxide, and fenamiphos sulfone (OPPTS Guideline 860.1300).

The nature of the residue in ruminants is adequately understood. The major residues identified in ruminant tissues and milk consisted of fenamiphos sulfoxide phenol, fenamiphos sulfoxide, fenamiphos sulfoxide phenol sulfate, fenamiphos sulfone phenol sulfate, fenamiphos phenol sulfate, des-isopropyl fenamiphos sulfoxide (in milk only), and des-isopropyl fenamiphos sulfone (in muscle only). Currently, the terminal residues of concern are fenamiphos, fenamiphos sulfoxide, fenamiphos sulfone, des-isopropyl fenamiphos, des-isopropyl fenamiphos sulfoxide, and des-isopropyl fenamiphos sulfone. The proposed metabolic pathway in ruminants is similar to that of plants with the exception of an additional de-isopropylation step. The qualitative nature of the residue in poultry is adequately understood. The residues of concern in poultry are fenamiphos, fenamiphos sulfoxide, fenamiphos sulfone, des-isopropyl fenamiphos, des-isopropyl fenamiphos sulfoxide, and des-isopropyl fenamiphos sulfone.

(ii). Analytical Methods

Adequate enforcement methods are available for the determination of residues of fenamiphos and its cholinesterase-inhibiting metabolites in/on plant and animal commodities. The Pesticide Analytical Manual (PAM) Vol. II lists two GLC methods, each with thermionic detection (TD) and a limit of detection (LOD) of 0.01 ppm. Method I (Bayer, Inc. Method 25402) is available for the determination of the combined residues of fenamiphos and its sulfoxide and sulfone metabolites, measured as sulfone, in/on plant commodities and Method II is available for the determination of the combined residues of fenamiphos, its sulfoxide and sulfone metabolites, des-isopropyl fenamiphos, des-isopropyl fenamiphos sulfoxide, and des-isopropyl fenamiphos sulfone in animal tissues and milk. The requirement for radiolabeled validation of the current enforcement methodology using representative samples from metabolism studies is waived because the enforcement analytical method has been validated and much is known about metabolism.

Residue data submitted in response to the Guidance Document and in support of petitions for the establishment of new tolerances were collected using modifications of the available PAM Vol. II methods. These modified methods, along with other methods listed in PAM Vol. II, are adequate for fenamiphos data collection and tolerance enforcement.

The FDA Pestrak database (PAM Vol. I, Appendix II) contains data concerning the applicability of all FDA multiresidue methods for recovery of fenamiphos and its sulfoxide and sulfone metabolites. Fenamiphos and its sulfoxide and sulfone metabolites are completely recovered through the Luke Method (232.2). Data pertaining to the multiresidue method testing of the des-isopropyl metabolites are no longer required (OPPTS Guideline 860.1340 and 860.1360).

(iii). Storage Stability

Storage stability data are adequate for plant commodities on Chinese cabbage (bok choy), eggplant, kiwifruits, non-bell peppers, and peanuts and their processed commodities. Storage stability data are also available for several commodities for which no tolerance has been established including corn, broccoli, potatoes, and carrots. Data have generally demonstrated stability of fenamiphos and metabolites for intervals up to 1170 days on some commodities.

Storage stability studies with asparagus, bananas, garlic, and the processed commodities of cottonseed and grapes will be used to fulfill the outstanding requirements for storage stability data on asparagus, bananas, Brussels sprouts, garlic, okra, and strawberries and the processed commodities of cottonseed, grapes, and pineapples. The representative data must be consistent with the storage intervals of commodities from magnitude of the residue and metabolism studies for both the commodities tested and commodities to which these data will be translated. Because all previous storage stability studies for both registered and unregistered commodities provide preliminary evidence of stability of fenamiphos residues in plant commodities, the outstanding data are considered confirmatory and the existing information sufficient to support the magnitude of residue studies and the tolerance reassessments.

Storage stability data have been submitted for milk samples and tissue extracts. Tissue samples from feeding studies were stored for a short interval prior to extraction, but the extracts were stored for an extended period. Studies have indicated that fenamiphos and des-isopropyl fenamiphos are oxidized to the corresponding sulfoxide in extracts. Since the conversion is quantitative and the oxidation product is regulated, instability does not affect the results of the feeding studies. Studies have also determined that the des-isopropyl sulfoxide in liver and des-isopropyl sulfone in kidney and fat are converted to the corresponding fenamiphos phenolic metabolite when stored in extracts. Residues of the remaining metabolites in tissues (stored in extracts) and all residues in milk have been found to be stable for the storage intervals from the feeding studies, up to 90 days. No additional storage stability data are required to support the existing feeding studies (OPPTS Guideline 860.1380).

(iv). Magnitude of the Residue in Raw Agricultural Commodities and Processed Food/Feed

All data requirements for magnitude of the residue in plants have been evaluated and deemed adequate to reassess the tolerances for residues of fenamiphos; additional data are required however for cotton gin by-products. Field trials were performed representing the various conditions under which the pesticide could be applied. The geographical representation for each commodity is generally adequate and a sufficient number of trials reflecting representative formulation classes were conducted. The recently submitted fenamiphos labels from countries that use fenamiphos on bananas targeted for export to the U.S. market are supported by adequate residue data. Cotton gin-by-products (considered a raw agricultural commodity) were added to Table 1 of OPPTS Test Guidelines, Series 860, Residue Chemistry, August, 1996, as an animal feed item, but data are not available for fenamiphos residues on this commodity. Lack of data regarding fenamiphos residues on cotton gin by-products will not affect the reregistration eligibility, but confirmatory data are required. The registrant must submit six studies reflecting residues of all regulated residues on cotton gin by-products; three trials each must be conducted reflecting harvesting by stripper and picker methods (OPPTS Guideline 860.1500).

Magnitude of the residue and pyrolysis studies have been submitted for tobacco. Sufficient data are available to assess residue levels of fenamiphos and metabolites in tobacco.

All data requirements for magnitude of the residue in processed food/feed have been evaluated and deemed adequate to determine the extent to which residues of fenamiphos concentrate in food/feed items upon processing of the raw agricultural commodity. Existing tolerances have been reassessed and found appropriate. Residues tend to concentrate in dried, processed feed items (grape pomace, apple pomace, citrus pulp, and raisin waste) and in citrus molasses. Residues also concentrate in raisins, and citrus oil.

(vi). Residues in Meat, Milk, Poultry, Eggs

Poultry. In light of the updated poultry metabolism study and a two-fold reduction in the theoretical dietary burden for poultry based on feed items listed in Table 1, Residue Chemistry Guidelines 860 Series dated August 1996, the Agency has reevaluated the need for additional poultry feeding studies. Due to the low level of toxicologically-significant residues transferred to poultry and eggs in the poultry metabolism study conducted at an exaggerated rate (28X), no detectable residues are expected in poultry and eggs from the presence of fenamiphos in/on livestock/poultry feed items. Thus, the use of fenamiphos on poultry feed items is considered a category of 40 CFR 180.6(a)(3); and, additional poultry feeding studies and tolerances for residues of fenamiphos in poultry meat and eggs are not required (Guideline 860.1480).

Ruminant. Ruminant feeding studies have recently been reevaluated and found to be adequate to satisfy ruminant feeding study data requirements. Two studies were conducted where cattle were fed fenamiphos or fenamiphos sulfoxide at levels ranging from 0.7 to seven times the maximum dietary burden. Residues were generally nondetectable in tissues and milk. The storage stability data to support this study remain outstanding. Because existing data provide preliminary evidence of stability of the residues, the available information is adequate to conclude that the established tolerances on livestock commodities are appropriate. However, many of the animal feed items used to estimate secondary residues in livestock commodities are no longer considered significant feed items in the most recent version of the Residue Chemistry Guidelines Table 1, 860 dated August 1996. Based on these revisions, the reassessed tolerances have been reconsidered, particularly for animal feed items, and meat and milk tolerances are no longer required.

A revised maximum dietary burden has been estimated using the reassessed tolerances and proposed tolerances.

Table 3. Maximum Dietary Burden for Dairy and Beef Cattle

Commodity	Maximum Residue (ppm)	% Dry Matter	Dairy % in Diet	Beef % in Diet	Max Dietary Burden (ppm) Dairy	Max Dietary Burden (ppm) Beef
Apple Pomace	1.22	40	20	40	0.61	1.22
Potato Waste [1]	0.4	15	40	40	1.07	1.07
Peanut Meal [2]	1.0	85	15	0	0.18	0.00
Citrus Pulp	2.5	91	20	20	0.55	0.55
TOTAL			*95.00*	*100.00*	*2.41*	*2.84*

[1] A tolerance for potatoes has been proposed, but has not yet been established. A tolerance has been proposed for almond hulls, but the contribution to the livestock diet would be minimal.

[2] HED has recommended for an increased tolerance to 1 ppm for peanuts. No concentration or reduction of residues has been observed in peanut meal (MRID 41255702).

Fenamiphos residues in animal commodities are regulated in terms of the parent, fenamiphos sulfoxide, fenamiphos sulfone, des-isopropyl fenamiphos, des-isopropyl fenamiphos sulfoxide, and des-isopropyl fenamiphos sulfone. Two feeding studies have been conducted with fenamiphos or one of its metabolites. In the first study cows were fed 4, 12, or 20 ppm fenamiphos in their diet. Tissues and milk were analyzed for residues of the parent, the sulfoxide, and sulfone. No residues were detected in milk or any tissue at all feeding levels. In the second study cows were fed fenamiphos sulfoxide in their diet at 2, 6, or 20 ppm, and samples were analyzed for all the regulated metabolites using a common moiety method. Residues were nondetectable in all tissues and milk at the 2 and 6 ppm levels. No residues were detected in milk and all tissues except liver in the 20 ppm study; residues in the liver were 0.012 ppm. The registrant tentatively identified the detectable residue as a des-isopropylated metabolite.

Extrapolating from the 20 ppm level to 2.8 ppm, there is a potential for residues of 0.0017 ppm in the liver. It is highly unlikely that a cow would ever eat a diet such as the one presented in
Table 3, above. Each of the feeds are likely to be fed in a specific region of the country, but it is very unlikely that all of these feed items would be produced in the same region. Additionally all of these feed items would usually be blended or diluted, so the residues in feed are not likely to be close to the maximum burden presented above.

When all parameters associated with this diet are taken into consideration, residues of fenamiphos and metabolites will not be detected in livestock commodities. There is no reasonable expectation of finite residues of fenamiphos and metabolites in livestock commodities as well. Therefore, HED now considers this to be a 40 CFR §180.6(a)(3) situation, and that all tolerances for meat and milk should be revoked. Should the registrant propose tolerances for additional feed items, then the need for meat and milk tolerances will have to be reconsidered.

(vii). Magnitude of the Residue - Rotational Crops

The submitted confined rotational crop study is adequate to satisfy the OPPTS Guideline 860.1850 requirement for purposes of reregistration. The study indicates that ^{14}C-residues (expressed as fenamiphos equivalents) accumulated at levels >0.01 ppm in/on all commodities of beets, Swiss chard, and wheat that were planted 30, 120, and 269 days after ring-labeled [1-^{13}C/^{14}C]fenamiphos was applied to sandy loam soil at 1.1X the maximum registered rate for annual food/feed crops. Fenamiphos sulfone and fenamiphos sulfoxide, the two metabolites of concern (in addition to the parent), were the principal organosoluble residues identified from the 30-day rotations, and collectively accounted for 12-49% of the radioactivity; the proportion of these two residues declined at subsequent intervals. The parent, fenamiphos, was a minor (<1% of the Total Radiolabeled Residue (TRR)) residue at all intervals.

The limited field rotational study indicates that fenamiphos residues of concern were detected at levels >0.01 ppm in/on spinach leaves (0.03 ppm), sorghum forage (0.44 ppm), and straw (0.02 ppm) from the four-month rotation grown in test plots treated at 1X the maximum seasonal rate for annual crops.

To assure that residues of fenamiphos are not found in rotational crops, and to facilitate inclusion of rotational crop residues in dietary risk assessment, the registrant should either: (1) amend product labels to include an eight-month plantback interval so that residues of fenamiphos and its regulated metabolites will not be found in rotational crops, or (2) based on the limited field trial data, propose rotational crop tolerances for crops which are specified on product labels. If the registrant elects the latter, extensive field rotational crop studies will be required; these field trial data will be considered confirmatory (OPPTS Guideline 860.1850, 850.1900).

(viii). Anticipated Residues and/or Monitoring Data and Percent Crop Treated Information

The most refined dietary exposure analysis to date for fenamiphos is presented below. Percent of crop treated data supplied by BEAD in 1999 were used in this analysis (see attachment for BEAD's Quantitative Usage Analysis (QUA), T. Kiely, 3/1/99). The usage estimates for the QUA are based primarily on data from 1990-1996. These data indicate usage of fenamiphos on more sites than the previous estimates, but with fewer acres treated and pounds of a.i. applied.

Both acute and chronic anticipated residues were calculated using residue monitoring data from USDA's PDP and the FDA Surveillance Monitoring Program data. PDP data from 1994-1997 and FDA Monitoring data from 1995-1997 were used for all crops having reassessed tolerances. See Attachment 1 for details concerning calculation of anticipated residues for the dietary exposure analyses. With the exception of three samples (two grape and one strawberry), all 26,619 samples analyzed by PDP and FDA (for the above noted time periods) for fenamiphos and its regulable metabolites had nondetectable residues.

PDP

USDA's PDP was created in 1991 to collect data on pesticide residues in foods. PDP monitoring data was specifically designed for use in dietary risk assessment. PDP's sampling procedures are statistically apportioned according to state population. The samples are collected at terminal markets and warehouse distribution centers which are closer to the supermarket, and eventual consumption, than the "farmgate." PDP's analytical laboratory procedures emphasizes searching for PDP-required pesticide residues at the lowest possible limits of detection. Their QA/QC (quality assurance/quality control) protocols, which are based on the Agency's Good Laboratory Practices (GLPs), are designed to ensure the reliability of PDP monitoring data. Prior to analysis, commodities are prepared (*i.e.*, washed or peeled) to mimic normal consumer practices.

FDA Monitoring

FDA monitoring data are also available for fenamiphos and its regulated metabolites. These data are available for all commodities sampled in the PDP program, and for many more commodities not sampled by PDP. The purpose of the FDA monitoring program is enforcement of tolerances, *i.e.*, to ensure that adulterated foods do not enter into commerce. Therefore, unlike PDP, FDA collects samples for analysis at the "farmgate." FDA also analyzes samples without washing, peeling or other consumer preparation practices. Therefore, if residues are present in or on a commodity, because of the temporal aspects and lack of washing and preparation, residues would be expected to be present at higher levels when FDA samples as opposed to when PDP collects samples.

The only commodities for which insufficient FDA or PDP monitoring data are available to calculate anticipated residues were garlic, kiwi, peanuts. For these commodities, residue field trial data were used to calculate chronic anticipated residues and/or the distribution of field trial results was used in the acute dietary exposure analysis.

Both PDP and FDA samples are composited samples, *i.e.,* approximately five pounds of the commodity are chopped and blended together from which the analytical sample is taken. Analytical results from these composited samples can be used by EPA in chronic dietary risk assessment, as the residues present in a composited sample are averaged across the sample and are highly reflective of the residues consumed on an average basis.

Because of the composited samples, use of PDP monitoring data directly in an acute dietary assessment has not previously been considered appropriate. Analyses of single-serving commodities, such as a single apple or potato, represent the highest concentrations that could be found in one serving of a commodity. It is these potentially high residues that are of concern for acute dietary risk assessments. Until now, EPA has used PDP monitoring data in acute dietary assessments only for blended commodities, such as apple sauce. Because of the blending that occurs when batches of apple sauce are made, use of average residues is appropriate.

Recently, Agency statisticians have developed a method using standard statistical procedures to adjust the composited residues to reflect residues that could be present, potentially, in single-serving sizes of commodities - making them suitable for acute dietary analyses. The methodology assumes the following: (1) the weight of the sample that was composited based on PDP Standard Operating Procedures regarding the amount of sample collected; (2) the number of units (such as apples or oranges) in the sample that was composited; and (3) the distribution of residues in the units is lognormal. This method yields a distribution of theoretical single-serving residues (based on the composited residues) that would have resulted if the residue analysis had been done on single-serving items without compositing.

However, because the monitoring data for fenamiphos from both USDA and FDA databases reported nondetectable residues for nearly all samples, the statistical method described above was not applied to residue data for fenamiphos. Instead, ½ LOD was used in the analysis for all residues corresponding to treated samples reporting nondetectable residues, and all residues corresponding to untreated samples will be assumed to have negligible residues. This is in accordance with current procedures requiring at least 30 samples with detectable residues prior to using standard statistical procedures to adjust the composited

residues to reflect residues that could be present, potentially, in single-serving sizes of commodities (see, Protocol for running Monte Carlo Assessments Using PDP and FDA Monitoring Data, draft, 2/22/99). When both PDP and FDA had data available for a commodity, the data set with the lower LOD (generally FDA data) was used for the dietary exposure analysis.

b. Dietary Risk Characterization - Food Sources

(i). Acute Dietary (Food) Exposure and Risk Estimates

Acute dietary (food) risk estimates do not exceed the Agency's level of concern.

The acute dietary analysis presented below is the most refined analysis to date for fenamiphos. As noted previously, percent of crop treated data supplied by BEAD in 1999 were used in this analysis. The exposure analysis was performed using the Dietary Exposure Estimate Model (DEEM™) which incorporates consumption data from the USDA's CSFII (1989-1992 data). As noted above, the anticipated residues used in this analysis were derived from residue monitoring data from USDA's PDP and the FDA Surveillance Monitoring Program data. Attachment 1 contains a detailed description of how anticipated residues were calculated for various commodities. Present policy (as presented at the TRAC meetings) concerning commodities having all nondetectable residues in monitoring programs dictates that another exposure analysis be conducted assuming zero residues present. If this assumption is made, then there is zero acute dietary exposure to fenamiphos.

As per current OPP policy, an RfD modified by an FQPA safety factor is referred to as aPAD. Because the FQPA safety factor was removed for fenamiphos, the acute and chronic RfD is equal to the acute and chronic PAD.

At the 99.9^{th} percentile exposure, acute dietary risk estimates do not exceed the Agency's level of concern. Table 4 summarizes the acute dietary (food) exposure and risk estimates for the U.S. Population, and infants and children. All other population subgroups had exposures less than the U.S. Population.

Table 4. Acute Dietary (Food) Exposure Estimate and Percent of Acute PAD Occupied for Fenamiphos

Population	90th Percentile		99th Percentile		99.9th Percentile	
	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
U.S. Population	0.000027	2	0.000097	8	0.000349	29
Nursing Infants (<1 yr)	0.000046	4	0.000494	41	0.000814	68
Non-nursing Infants (< 1 yr)	0.000089	7	0.000313	26	0.000521	43
Children 1-6 yr	0.000076	6	0.000304	25	0.000664	55
Children 7-12 yr	0.000034	3	0.000113	9	0.000282	24
Females 13+, nursing	0.000108	9	0.000227	19	0.000266	22
Males, 20+	0.000016	1	0.000054	4	0.000146	12

(ii). Chronic Dietary (Food) Exposure and Risk Estimates

Chronic dietary (food) risk estimates do not exceed the Agency's level of concern.

The chronic dietary analysis presented below is the most refined analysis to date for fenamiphos. Percent of crop-treated data supplied by BEAD in 1999 were used in this analysis. The exposure analysis was performed using the Dietary Exposure Estimate Model (DEEM™) which incorporates consumption data from the USDA's Nationwide Food Consumption Survey II (1989-1992 data). As noted above, the anticipated residues used in this analysis were derived from residue monitoring data from USDA's PDP and the FDA Surveillance Monitoring Program data. Attachment 1 contains a detailed description of how anticipated residues were calculated for various commodities.

Chronic dietary risk estimates do not exceed the Agency's level of concern. Table 5 summarizes the acute dietary (food) exposure and risk estimates for the U.S. Population, and infants and children, and those population subgroups with exposures higher than that of the U.S. Population. These dietary risks do not include rotational crop residues. If the eight-month plant-back interval is not enforced on the end-use labeling for rotational crops and tolerances were required, the dietary exposure and risk would be significantly increased as a result of rotational crop residues.

Table 5. Chronic Dietary (Food) Exposure and Risk Estimates for the U.S. Population, Infants and Children, and Subgroups with Higher Exposures that the U.S. Population

Population Subgroup	Exposure (mg/kg/day)	% cPAD
U.S. Population	0.000005	5
Nursing infants (<1 yr old)	0.000013	13
Non-Nursing infants (<1 yr old)	0.000014	14
Children (1-6 yrs)	0.000015	15
Children (7-12 yrs)	0.000006	6
Females (13+ yrs/nursing)	0.000014	14
Males, 20+	0.000002	2

c. Dietary Exposure - Drinking Water

The Office of Water has established the following Health Advisory Levels (HALs) for fenamiphos (EPA Drinking Water Regulations and Health Advisories, EPA 822-B-96-002, October, 1996). For a 10 kg child, the one-day and 10-day HALs are 0.009 mg/L (9 ppb), and the longer term HAL is 5 ppb. For a 70 kg adult, the longer term HAL is 20 ppb and the lifetime HAL is 2 ppb.

Since the previous HED RED chapter was drafted (Memo dated 10/17/97, E. Waldman) EFED has provided HED with a revised drinking water assessment. Accordingly, the HED risk estimates for drinking water have been revised to reflect these revised risk estimates and current OPP water policy since the passage of FQPA.

Because of its chemical characteristics, fenamiphos is a pesticide that will leach to groundwater and/or runoff in vulnerable areas. Parent fenamiphos is relatively mobile with Kd values in four soils ranging from 0.95 to 3.4 ml/g, and K_C values from 166 to 543. From laboratory studies, the sulfoxide and sulfone metabolites are more mobile than the parent. Parent fenamiphos has the potential to be moderately persistent under certain conditions. Although the aerobic half-life is short, the anaerobic soil metabolism half-life for the parent is approximately 88 days (13 weeks) which indicates that it will persist once it reaches most groundwater. Persistence data are incomplete for both fenamiphos sulfoxide and sulfone. Both degradates have been detected in groundwater in Florida, indicating that they are both sufficiently persistent to leach in some environments.

In accordance with present policy (OPP's Interim Approach for Addressing Drinking Water Exposure), quantitative risk estimates for pesticide exposure in drinking water are only calculated when appropriate and reliable monitoring data are available. In cases where appropriate and reliable monitoring data are not available, modeling information is used to estimate the concentration of a pesticide in drinking water. The primary use of these models by OPP at this stage is to provide a coarse screen for sorting out pesticides for which it is highly unlikely that drinking water concentrations would ever exceed human health levels of concern.

As discussed below, in the case of fenamiphos, high-quality monitoring data are available for the parent and the sulfoxide and sulfone degradates for groundwater. OPP has limited data on the concentrations of fenamiphos in surface water. Monitoring for fenamiphos in south Florida at 27 surface-water sites did not yield any detections and results of a STORET search indicated fenamiphos was not detected in any of the samples at detection limits ranging from 0.04 to 0.75 ppb. However, no information is available to determine if fenamiphos is used in the areas tested for fenamiphos. Therefore, EFED has little confidence in the monitoring data available for surface water and recommends the use of modeling numbers for comparison to a DWLOC for fenamiphos in surface water.

Currently, HED uses DWLOCs as a surrogate to capture risk associated with exposure to pesticides in drinking water. A DWLOC is the concentration of a pesticide in drinking water that would be acceptable as an upper-limit in light of total aggregate exposure to that pesticide from food, water, and nonoccupational uses (if any). A DWLOC may vary with drinking water consumption patterns and body weights for specific subpopulations.

(i). Groundwater

OPP has high-quality monitoring data for the parent and the sulfoxide and sulfone degradates in groundwater and has high confidence in the concentrations used in this risk assessment. Acute and chronic concentrations are given for fenamiphos, fenamiphos sulfoxide, and fenamiphos sulfone in groundwater that could be used for drinking. Also presented in this risk assessment are the acute and chronic concentrations for the total of these three toxic compounds in groundwater-source drinking water.

Data from studies in a hydrogeologically vulnerable area of Florida (the Central Ridge) indicate that fenamiphos residues leach to groundwater as a result of normal agricultural use. In a small-scale prospective study conducted in Florida, fenamiphos, fenamiphos sulfoxide, and fenamiphos sulfone concentrations up to 0.58, 83.31 and 3.32 ppb, respectively, were detected in groundwater that could be used for drinking. Total residues in one sample ranged up to 87.2 ppb.

In another study conducted in Florida, concentrations were significantly higher and ranged up to 22.5 ppb, 204 ppb, and 19.9 ppb for the parent, sulfoxide degradate, and sulfone degradate, respectively. The highest level of total residues detected in groundwater during one sampling event in this retrospective study was 239 ppb.

Another prospective study is ongoing in a tobacco growing site in Georgia. Preliminary results indicate that fenamiphos sulfoxide was detected in two shallow wells at concentrations of 0.06 and 0.25 ppb. No fenamiphos parent or fenamiphos sulfone was detected at greater than the 0.05 ppb Limit of Quantitation. The information from this study is not used in this assessment because the study is ongoing and all results are preliminary as of October 1997.

The acute concentrations provided below are the highest levels seen in any well during the Florida study and are believed to be representative of groundwater that is currently or could reasonably be expected to be a source of drinking water.

The chronic concentrations were determined by using all values from all the onsite wells during a 90-day monitoring period. This particular time frame was selected from all monitoring information after determining the 90-day period when the highest concentrations were seen. The average of all these values was taken to get the chronic concentration, including half the 0.1 ppb Limit of Detection or 0.05 ppb when no fenamiphos residues were reported. Concentrations are reported for fenamiphos, fenamiphos sulfoxide, and fenamiphos sulfone; the total for these toxic analytes is also given.

Acute values (potential drinking water source):

total fenamiphos residues: 87.2 ppb
fenamiphos parent: 0.6 ppb
fenamiphos sulfone: 3.3 ppb
fenamiphos sulfoxide: 83.3 ppb

Chronic values (90-day average):

total fenamiphos residues: 9.9 ppb
fenamiphos parent: 0.1 ppb
fenamiphos sulfone: 0.3 ppb
fenamiphos sulfoxide: 9.5 ppb

HED has prepared a quantitative exposure and risk assessment using the monitoring data provided by EFED. HED calculates the drinking water exposure using values provided by EFED. The following equations are used:

$$\text{Exposure (mg/kg/day)} = \frac{\text{conc. water(ug/L)} \times 10^{-3}\,\text{(mg/ug)} \times 2\text{L/day}}{70\text{ kg for adults (male)}}$$

$$\text{Exposure (mg/kg/day)} = \frac{\text{conc. water (ug/L)} \times 10^{-3}\,\text{(mg/ug)} \times 2\text{L/day}}{60\text{ kg for adults (female)}}$$

$$\text{Exposure (mg/kg/day)} = \frac{\text{conc. water (ug/L) x } 10^{-3}\text{ (mg/ug) x 2L/day}}{\text{10 kg for children}}$$

For exposure calculations, HED used the concentration values for total fenamiphos residues for the acute high value and chronic value (discussed above) to determine the acute and chronic exposure, respectively. Exposure estimates for the total residues of fenamiphos (fenamiphos and metabolites) in groundwater are presented in Table 6. These estimated were obtained from the concentration values provided by EFED and the formulas described above.

Table 6. Exposure Estimates for the Total Residues of Fenamiphos in Groundwater

Subpopulation	Acute Exposure (mg/kg/day)	Chronic Exposure (mg/kg/day)
Males	0.002	0.0003
Females	0.003	0.0003
Children	0.009	0.001

(ii). Surface Water

OPP has limited data on the concentrations of fenamiphos in surface water. Water supply systems are not required to sample and analyze for fenamiphos as it is not currently regulated under the Safe Drinking Water Act. Monitoring for fenamiphos in south Florida at 27 surface water sites did not yield any detections. The detection limits were relatively high and ranged from 0.6 to 1.6 ppb. A STORET search resulted in a listing of 37 samples over 20 sites in three states. Fenamiphos was not detected in any of the samples at detection limits ranging from 0.04 to 0.75 ppb. No information is provided in STORET about whether samples were taken from fenamiphos use areas. Therefore, EFED has little confidence in the monitoring data available for surface water and recommends the use of modeling numbers to calculate a DWLOC for fenamiphos in surface water.

Fenamiphos has the potential to contaminate surface water via spray drift, ground tile drainage flow, and runoff. The typical incorporation of fenamiphos into the soil should limit the fraction available for runoff. However, relatively high application rates, coupled with only moderate susceptibility to biodegradation, may make substantial quantities of fenamiphos that are within approximately the top centimeter of soil remain available for runoff for several weeks postapplication. Its' relatively low soil/water partition coefficient coupled with typically much higher runoff volumes than soil loss indicates that runoff will be primarily via dissolution in runoff water rather than adsorption to eroding soil.

An anaerobic soil metabolism half-life of greater than 60 days indicates that fenamiphos may be substantially more persistent in a typically anaerobic sediment/lower water column than in the typically aerobic upper water column. The soil/water partitioning of fenamiphos indicates that its concentration in sediment pore water at equilibrium will be comparable to or somewhat lower than its concentration adsorbed to suspended and bottom sediments.

The sulfoxide and sulfone degradates appear to be at least as persistent and more mobile than fenamiphos and may have at least comparable toxicity to nontarget organisms. Therefore, the sulfoxide and sulfone degradates are also of concern for surface water and surface-source drinking water.

Tier I GENEEC modeling was used for 25 crops and Tier II PRZM/EXAMS was used for the five additional use crops. Fenamiphos is used on several crops with large acreage in the United States. In addition, use of fenamiphos on several of these crops could have a potentially significant impact on surface water used for drinking because of the soil types, hydrologies, etc. These crops include apples, citrus, cotton, and turf. Although fenamiphos is not widely used on some of these crops, the correlation between high use and detections in water resources is very tenuous and, therefore, the impact could be high although the use is low. Presented below in Table 7 are the predicted concentrations for the four crops (apples, citrus, cotton, and turf).

Table 7. Predicted Concentrations of Fenamiphos in Surface Water

Crop	Model	Acute Concentration peak value (ppb)	Chronic Concentration 90-day value (ppb)
Apple	GENEEC	105.4	53
Citrus	GENEEC	105.4	53
Cotton	PRZM/EXAMS	112	46.7
Turf	GENEEC	651	329

GENEEC is a screening model designed to estimate surface water concentrations to use in ecological risk assessments. As such, it provides upper-bound concentrations that might be found in ecologically sensitive environments because of the use of a pesticide. GENEEC is a single runoff event model that can account for spray drift from multiple applications. GENEEC is hardwired to represent a 10-hectare field immediately adjacent to a one-hectare pond that is two meters deep with no outlet. The pond receives a spray drift event from each application plus one runoff event. The runoff event moves a maximum of 10% of the applied pesticide into the pond. This amount can be reduced by degradation and soil binding in the field. Spray drift is equal to 1% of the applied rate for a ground spray application.

GENEEC provides an upper-bound estimate on the concentration of pesticide that could be found in drinking water and therefore can be appropriately used in screening calculations. If a risk assessment performed using GENEEC output does not exceed the level of concern, then one can be reasonably confident that the risk will also be below the level of concern. However, since GENEEC can substantially overestimate true drinking water concentrations, it will be necessary to refine the GENEEC estimate if the level of concern is exceeded. The EECs do not reflect the concentration of any fenamiphos degradates.

d. Dietary (Drinking Water) Risk Characterization

As discussed above, quantitative risk estimates for pesticide exposure in drinking water are only calculated when appropriate and reliable monitoring data are available. In the case of fenamiphos, high-quality monitoring data are available for the parent and the sulfoxide and sulfone degradates for groundwater only. Therefore, only risk estimates will be calculated for acute

and chronic drinking water risk from groundwater.

(i). Groundwater - Acute Dietary Risk Estimates

The acute RfD of 0.0012 mg/kg for fenamiphos was derived from a LOAEL of 0.37 mg/kg/day established in an acute neurotoxicity study based on inhibition of plasma and red blood cell cholinesterase activity and an UF of 300.

The acute dietary (groundwater) risk estimates for fenamiphos calculated from the groundwater exposure values (see Table 6) and the acute RfD are presented in Table 8.

Table 8. Acute Dietary Risk Estimates for Fenamiphos in Groundwater

Population Subgroup	Exposure (mg/kg/day)	% aPAD[1]
Males	0.002	170%
Females	0.003	250%
Children	0.009	750%

[1]% aPAD = Exposure/aPAD x 100

The acute dietary risk estimates for groundwater exceed the Agency's level of concern (*i.e.*, in excess of 100% of the aPAD) . However, the consumption of drinking water obtained from groundwater at various sites in Florida that are hydrogeologically vulnerable are considered a high-exposure scenarios for the parent, fenamiphos and its metabolites. If water were to be obtained solely from this source (containing total fenamiphos residues at 87.2 ppb), 100% of the aPAD would be exceeded for males, females, and children. There are limitations to these risk estimates (*e.g.,* the data are from groundwater wells versus directly from the tap). However, as stated earlier EFED is confident in the groundwater concentrations reported.

(ii). Groundwater - Chronic Dietary Risk Estimates

The chronic RfD of 0.0001 mg/kg/day for fenamiphos was derived from a NOAEL of 0.01 mg/kg/day established in a chronic feeding study in dogs based on plasma cholinesterase inhibition at 0.03 mg/kg/day and an UF of 100.

The chronic dietary (groundwater) risk estimates for fenamiphos calculated from the groundwater exposure values (see Table 6) and the cPAD are presented in Table 9.

Table 9. Risk Estimates for the Total Residues of Fenamiphos in Groundwater

Subpopulation	Chronic Exposure (mg/kg/day)	% cPAD
Males	0.0003	300%
Females	0.0003	300%
Children	0.001	1000%

[1]% cPAD = Exposure/chronic PAD x 100

The chronic dietary risk estimates for groundwater exceed the Agency's level of concern. However, the consumption of drinking water obtained from groundwater at various sites in Florida that are hydrogeologically vulnerable are considered high-exposure scenarios for the parent, fenamiphos plus its' metabolites. If water were to be obtained solely from this source (containing total fenamiphos residues at 9.9 ppb), 100% of the cPAD would be exceeded for males, females, and children. There are limitations to these risk estimates (*e.g.,* the data are from groundwater wells versus directly from the tap). However, as stated earlier EFED is confident in the groundwater concentrations reported.

(iii). Surface Water - Drinking Water Levels of Comparison

Currently, when high-quality monitoring data are not available, HED uses DWLOCs as a surrogate to capture risk associated with exposure to pesticides in drinking water. A DWLOC is the concentration of a pesticide in drinking water that would be acceptable as an upper-limit in light of total aggregate exposure to that pesticide from food, water, and nonoccupational uses (if any). A DWLOC may vary with drinking water consumption patterns and body weights for specific subpopulations.

DWLOCs were calculated and compared to model estimates of fenamiphos concentrations in surface water. Based on the acute (99.9th percentile) and chronic dietary exposure estimates presented above, DWLOCs were calculated using the formulas presented below.

$$DWLOC_{acute} = \frac{acute\ water\ exposure\ (mg/kg/day) \times body\ weight\ (kg)}{consumption\ (L) \times 10^{-3}\ mg/ug}$$

where,

acute water exposure (mg/kg/day) =
aPAD -acute food exposure (mg/kg/day)

$$DWLOC_{chronic} = \frac{chronic\ water\ exposure\ (mg/kg/day) \times body\ weight\ (kg)}{consumption\ (L) \times 10^{-3}\ mg/ug}$$

where,

chronic water exposure (mg/kg/day) =
cPAD -chronic food exposure (mg/kg/day)

The Agency's default body weights and consumption values used to calculate DWLOCs are as follows: 70 kg/2L (U.S. Population) and 10 kg/L (child).

(iv). Surface Water - Acute DWLOC

For the 99.9th percentile dietary (food) exposure level, the acute DWLOC for adult males is 37 ppb, for adult females 28 ppb, and for nursing infants less than one year old (i.e., the most highly exposed (food) infant/children subgroup) it is 4 ppb.

(v). Surface Water - Chronic DWLOC

Based on the chronic dietary exposure estimates, the chronic DWLOC adult males and females is 3 ppb and for children 1-6 years old (the most highly exposed (food) infant/children subgroup) it is 1 ppb.

The EFED modeling estimates exceed both the acute and chronic DWLOCs for adult males, females, and the most highly exposed infant and children subgroups.

4. Occupational Exposure Assessment and Risk Characterization

a. Occupational Handler Exposure

Exposure data requirements are triggered based on the potential for exposure and the toxicological significance of the active ingredient. Exposure analyses for the use/activity patterns associated with fenamiphos have been completed for each handler (*i.e*., mixer/loader/applicator) scenario of concern; associated data gaps for specific exposure scenarios have been identified.

In addition, occupational exposure has been determined using mitigation techniques implemented by the registrant to reduce the exposure and the risk to workers involved with the use of this chemical.

(i). Mixer/Loader/Applicator Exposure Assessment

End-use product formulations include granulars and emulsifiable concentrates. The granular formulations contain 10 and 15 percent active ingredient. The emulsifiable concentrate formulation contains 35 percent active ingredient.

Applications can be made using ground equipment or chemigation. Additionally, a majority of the available labels preclude the use of any knapsack/backpack type equipment. Application types include: chemigation (*i.e*., low-pressure irrigation and solid-set irrigation); soil band treatments (*i.e*., granulars and emulsifiable concentrates); broadcast treatments (*i.e*., granulars and emulsifiable concentrates); in-furrow treatments; soil injection; and spray/foliar treatments. A majority of the labeled uses require that the applications are soil incorporated and/or watered-in via

irrigation or natural rainfall. Additionally, the timing for a majority of applications is at or near planting or the dormant stage for most of the labeled targets (*i.e*., timing for most application scenarios: posttransplant, postharvest, preemergence, pretransplant, preplant, or at planting). Chemigation application rates (*i.e*., EC formulation only) range up to 4.5 lb ai/acre for typical low-pressure irrigation and up to 12 lb ai/acre for solid-set irrigation techniques. Rates for ground-based applications of the emulsifiable concentrate formulations range up to: 20 lb ai/acre for broadcast applications; 10 lb ai/acre for soil banding and spray applications; 3 lb ai/acre for soil injection applications and 2.175 lb ai/acre for in-furrow treatments. Rates for the ground-based application of the granular formulations range up to: 10.05 lb ai/acre for banding (*i.e*., other banding rates were specified based on the row length -- maximum reported was 0.1725 lb ai/1000 linear feet); and 10 lb ai/acre for broadcast and in-furrow applications.

Data quality is a critical parameter in the interpretation of the results of any exposure assessment. No chemical specific mixer/ loader/applicator exposure data were previously required to support the reregistration of fenamiphos. Handle exposure risk assessments were conducted using the surrogate data from the Pesticide Handlers Exposure Database (PHED) database, Version 1.1.

Based on the current use patterns several exposure scenarios are plausible as defined by the types of application equipment and procedures that might be employed by fenamiphos handlers. Since the estimated occupational acres treated per day are low for many of the crops (as per the registrant), compared to standard default acreage used by HED, these risk assessments are considered to be refined.

Each scenario was defined by the types of potential mixing/ loading and application equipment that could be employed based on the major use groups for fenamiphos. The crop-specific maximum application rates (lb ai/acre) and maximum number of acres treated per day were provided by the registrant to SRRD (memorandum dated August 14, 1996, Melvin K. Tolliver, Regulatory Affairs Specialist). Exposure values were calculated based on PHED data. No chemical-specific handler exposure data were provided by the registrant. Summary of occupational exposure values that depict the handler exposure risk assessment using surrogate data from PHED Version 1.1 are presented in Table 10, which is located at the end of this risk assessment.

The caveats and parameters specific to each exposure scenario are summarized in Table 11 (which is at the end of this risk assessment). "Standard Assumptions" represent the use scenarios employed by HED to estimate daily exposure levels and are based on the use data presented by the registrant. The "Comments" section includes any other critical descriptions of the data including information pertaining to the quality of the exposure data, level of confidence, and any protection factors applied to the exposure data.

Data contained in PHED are assigned grades (A through E) based on the overall quality of the analytical recovery data generated concurrently with actual data points (*i.e.*, laboratory recovery, field recovery and stability data). All PHED-based exposure assessments were based on the surrogate unit exposure values currently being used as a standard source of exposure values, and the use data presented by the registrant. Values were defined using high-quality data and a large number of replicates to calculate exposures if the data were available. However, if not available, rangefinder exposure values were calculated using all data available in PHED.

In accordance with the existing use patterns, it is not expected that occupational exposures would occur for more than 90 days, which would result in chronic worker exposure. Therefore, a chronic exposure assessment is not required since chronic exposure is not expected. The pending registrations reflected in the registrant's submission are not considered for this reregistration exposure assessment.

The risk assessments for handlers raise the following concerns:

- The acres treated per day as presented by the registrant are substantially lower than those typically used by HED for the indicated exposure scenarios. Therefore, HED defers the verification of these values to the BEAD. The acres treated per day, as indicated by the registrant, are utilized for the purposes of reregistering fenamiphos. To date, BEAD has not verified the acreage values supplied by the registrant. Once the acreage is verified, the product labels should be modified to indicate the appropriate acreage restrictions. This will increase the label complexity significantly.

- Since the estimated acres treated per day are low for many of the crops, it is reasonable to assume that the mixing/loading, and application tasks may be performed by one person and, therefore, perhaps the assessment should combine the mixer/loader and applicator exposures for each crop grouping. HED defers combining the assessments pending confirmation by BEAD concerning the number of acres treated per day.

- Since the mitigation techniques necessary to adequately mitigate the risk are specific by crop (due to the differences in application rates and estimated acres treated per day), the labeling will have to list the required personal protective equipment (PPE) and/or engineering control by crop. To the Agency's knowledge, such an approach has never before been attempted and will add extraordinary complexity to the pesticide labeling. Ordinarily, HED uses standardized estimates of acres treated per day by equipment type. For example, HED estimates that a maximum of 80 acres per day can be treated by groundboom equipment. Within equipment-types, HED will then conduct the risk calculations based either on: (1) one maximum use-rate per acre for all crops or; (2) if there is a wide-range of use-rates for a formulation, on a range of use-rates, such as a

"typical" rate and a "maximum" rate.

(ii). Mixer/Loader/Applicator Risk Assessment

The MOEs for workers involved with mixing/loading and applying these chemicals on a short- or intermediate-term basis are estimated by the following equation:

$$MOE = \frac{NOAEL\ (mg/kg/day)}{Daily\ Dose\ (mg/kg/day)}$$

For fenamiphos, an MOE greater than 100 does not exceed the Agency's level of concern for all occupational exposure risk assessment. The MOEs for occupational exposure are summarized in the tables described below; the actual tables are at the end of this risk assessment.

- Table 12. Summary of Dermal Occupational Baseline Margins of Exposure (MOEs) and Risk Mitigation for Fenamiphos
  - presents the handler risk assessment via the dermal route -- with and without risk mitigation techniques
- Table 13. Summary of Inhalation Occupational Baseline Margins of Exposure (MOEs) and Risk Mitigation for Fenamiphos
  - presents the handler inhalation risk assessment with and without risk mitigation techniques
- Table 14. Summary of Occupational Dermal and Inhalation Margins of Exposure
  - provides an overall conclusion of the risk assessment

There are no data for the soil injection exposure scenario; therefore, an assessment was not conducted, and this scenario is not presented in Table 10. With the exceptions of loading the granular formulation and the tractor-drawn granular application exposure scenarios, there was high confidence in the baseline unit dermal and inhalation exposure values used from PHED Version 1.1 (There was low confidence in the dermal data and high confidence in the inhalation data used for the loading granulars scenario, and low confidence in both the dermal and inhalation data used for the tractor-drawn granular application scenario).

Tables 12, 13, and 14 provide an overall snapshot of worker risk estimates to fenamiphos indicating the range of MOEs for each route of exposure. Since there were several scenarios for which the MOEs were the same (less than 100, *i.e.*, <1), the site which resulted in the lowest MOE when additional mitigation measures were added was the site for which the MOE was presented in the table. The data in Table 14 depicts the lowest MOE for each scenario that is below 100 based on the dermal and the inhalation MOEs for each scenario. The data in Table 15 addresses the aggregate occupational exposure of dermal plus inhalation MOEs for occupational exposure.

HED raises the following concerns relative to estimating worker risk to fenamiphos:

- For the loading of granular formulation to support application to turf, the MOE is greater than 100 only with the use of engineering controls. The engineering control for loading granules is either a "lock and load" or "smart-box," but HED is uncertain whether equipment used for turfgrass applications is available that would support this technology. An alternative might be to require a more expensive/ elaborate respirator (see next bullet). HED also notes that these engineering controls are patented technologies and may not be available to the registrant or may be available only at considerable expense.

- For the application to turf with a tractor-drawn granular applicator, the inhalation MOE is less than 100 (i.e., 61), even with the use of engineering controls (enclosed cab). It is theoretically possible to

obtain an MOE of greater than 100 by requiring the use of a more protective (which is a more expensive and elaborate) respirator. For example, a powered-air-purifying respirator (PAPR) has a protection factor of 25, which would bring the MOE to 175 and a full-face respirator with a protection factor of 50 would bring the MOE to 350. However, neither of these respirators are considered common in agricultural, golf-course, or other turf settings. Furthermore, with the use of any respirator, a Respiratory Protection Program (which must include: medical clearance for each respirator wearer, fit-testing, training, respirator maintenance, etc.) is required, and must be in place prior to any issuance of any type respirator (see OSHA 29 CFR 1910.34, for further details). Any respirator utilized must be one approved respirator by MSHA/NIOSH.

(iii). Summary of Handler MOEs

The results of the agricultural handler assessments indicate that all but two commodities of the potential loader and tractor-drawn applicator exposure scenarios for a granular formulation provide aggregate (dermal + inhalation) MOEs less than 100 at baseline attire (*i.e*., long-pants, long-sleeved shirts, no gloves) and therefore, exceed the Agency's level of concern. The two commodities in these baseline scenarios that do not exceed the Agency's level of concern [aggregate (dermal + inhalation) MOEs greater than 100] are strawberries and eggplant. The cause of the aggregate MOEs being below 100 is primarily due to inhalation exposure.

Using engineering controls, all of the commodities evaluated within these scenarios have aggregate MOEs that are above 100, and therefore do not exceed the Agency's level of concern, except for tractor-drawn granular application to turf (MOE = 44).

The aggregate MOEs for all commodities within baseline mixer/loader scenarios (groundboom and chemigation) for a liquid formulation were less than 100, and therefore exceed the Agency's level of concern. The cause of the aggregate MOEs being below 100 is primarily due to dermal exposure.

Using engineering controls, most of the commodities

evaluated within these scenarios have aggregate MOEs that are above 100, and therefore do not exceed the Agency's level of concern, except for 12 commodities (apples, cherries, citrus, nectarines, peaches, grapes, tobacco, pineapples, turf, pome/stone/citrus fruit, kiwi, and ornamental nonflowering plants) where the aggregate MOEs range from 37 to 80.

The aggregate MOEs for all commodities within the baseline groundboom applicator scenario for a liquid formulation were less than 100 (range from 10 to 82), and therefore exceed the Agency's level of concern except for five commodities (beets, asparagus, eggplant, strawberries, and raspberries). The cause of the aggregate applicator MOEs being below 100 is primarily due to inhalation exposure.

Using engineering controls most of the commodities evaluated within this scenario have aggregate MOEs that are above 100, and therefore do not exceed the Agency's level of concern, except for eight commodities (apples, cherries, citrus, nectarines, peaches, grapes, tobacco, and turf) where the MOEs range from 53 to 86.

For soil injection, there are no data available.

b. Postapplication and Reentry

(i). Occupational Exposure Assumptions and Risk Characterization:

To be effective, fenamiphos should be mechanically incorporated or irrigated into the soil immediately after treatment and, with the exception of pineapples, it is not directed at foliage (even though foliage may be present during application). Therefore, postapplication exposure is mostly a concern for human activities which may involve contact with the soil after treatment (*e.g.,* applied just prior to transplanting strawberries).

The Registration Standard (1987) indicated that reentry data were required. About a year later, the registrant requested a waiver of the data requirements and of the proposed 48-hour reentry interval for the golf course use. Previously the Agency granted a waiver for both a data requirement and the 48-hour reentry for the golf course use. However, in light of FQPA, the data waiver previously granted for golf courses is no longer applicable. The registrant needs to provide a TTR study for golf course turf to refine postapplication exposure estimates.

Data are being required for uses which may result in workers handling or working with or in the treated soil, (*i.e.*, strawberries, asparagus, ornamental nonflowering plants, ornamental herbaceous plants, sod farm turf, ornamental woody shrubs and vines, and all nursery stock) to determine the appropriate REI.

Entry onto golf courses by employees should be restricted until the turfgrass has dried following the prescribed watering-in.

The Agency has reviewed a DFR study submitted on pineapples in support of reregistration requirements (Guideline 132-1(a); MRID 41901701). Results of this risk assessment are presented in Table 16. The study entitled, "Foliar Residue Following Application of NEMACUR to Pineapples" was submitted by Mobay Corporation. It was conducted on three sites in Hawaii using Nemacur 3 (EC). Based on the data analysis and toxicology data, a 17-day restricted entry interval (REI) was proposed by the registrant. The study is considered acceptable. The Agency concurs with the registrant's proposed restricted entry interval of 17 days for foliar applications to pineapples. At a 17-day REI or more, the harvester/worker's exposure does not exceed the Agency’s level of concern (i.e., MOE =110). Workers' exposure exceed the Agency’s level of concern from the day of application to 16 days after application (MOEs range from eight to less than 100).

The Agency is requiring a 17-day REI following foliar applications to pineapple. For all other use sites within the scope of the WPS (see PR Notice 93-7), where fenamiphos is incorporated into the soil either mechanically or through watering-in, the Agency is requiring a 48-hour restricted entry interval (REI). During the REI, the Agency will allow workers to enter areas treated with fenamiphos only in the few narrow exceptions allowed in the WPS. The 48-hour REI is being established based on: (1) classification of fenamiphos active ingredient as toxicity category I for acute dermal toxicity; (2) concerns about other adverse effects (cholinesterase inhibition); and (3) the fact that, unlike the foliar application to pineapple, the applications are immediately incorporated into the soil mechanically or through watering-in.

The Agency is requiring data and/or further clarification of the use patterns involving workers handling or working with or in the treated soil which may result in postapplication exposure. These uses are on strawberries, asparagus, ornamental nonflowering plants, ornamental herbaceous plants, sod farm turf, ornamental woody shrubs and vines, and all nursery stock. For these sites the 48-hour REI will be required, until receipt and evaluation of the additional data. The Agency requires confirmation that the golf course use does not result in postapplication exposure as a result of handling treated grass clippings.

(ii). Nonoccupational Exposure Assumptions and Risk Characterization

The potential for postapplication homeowner exposure exists for short- and intermediate-term time periods only. For example, potential exposures would be expected following applications to golf course lawns. Because there are no chemical-specific data to use in assessing these potential exposures, a rangefinder postapplication exposure and risk assessment was performed. Results of this risk assessment are presented in Table 17.

The assessment uses typical transfer coefficients (Tc); for golfers, the Tc is 1,00 cm^2/hr. Golfing (18 holes) – for a time period of four hours – is considered an activity with low potential for dermal transfer. In addition to Tc, the assessment also utilizes DFR of one and five percent of the application rate. The DFR percentage used is less conservative than the default 20 percent; which is based on foliar wash. However, the five percent is still much more conservative than the California Roller Method study, which had an average of 1-2% dislodgeable foliar residues available from application rates that were applied. EPA believes that exposures following golf course turf applications are likely to represent a reasonable postapplication exposure estimate to golfers. Nonoccupational exposure assumptions are from HED's Draft Residential SOPs, December 1997 version.

The postapplication exposure MOEs for short-term exposures for both golf exposure scenarios are:

- Adult: 78
- Adolescent12+: 49

Both exceed the Agency's level of concern.

This surrogate postapplication range finder exposure assessment was only performed for adult and adolescent golfers, who have a minimal amount of potential dermal contact/transfer from turf. Because the MOEs for adult and adolescent golfers exceed the Agency's level of concern, HED assumes that all nonoccupational postapplication exposure scenarios pertaining to golf course turf are also considered to exceed the Agency's level of concern. If this exposure and risk assessment had yielded MOEs greater than 100, then additional risk assessments would have been performed for other exposure scenarios resulting from the golf course use (*e.g.*, adult, adolescent and toddler aggregate (dermal plus oral) exposures).

c. Incident Reports

(i). Incident Data System (IDS)

Please note that the following cases from the IDS do not have documentation confirming exposure or health effects unless otherwise noted.

Incident 3913-1 and Update Incident 4446-1

A pesticide incident occurred in 1996, when fenamiphos was applied to citrus trees for three days and the applicator passed out and was admitted to a hospital for four days. He was still unable to work 10 days later. According to the report by the state enforcement agency, the unlicensed applicator was not monitored by his supervisor every two hours as required by the WPS and he was not provided and did not wear proper protective equipment. He did not wear protective eyewear, a chemical-resistant protective suit, and chemical-resistant gloves. The enforcement agency issued a fine for these violations. No further information on the disposition of the case was reported.

Incident 5244-1

A pesticide incident occurred in 1997, when a nursery worker was exposed while unloading a truck and got some powder in his left eye. He flushed his eye with water immediately and was seen by a doctor within a couple of hours. The doctor noticed an abrasion/burn to the cornea. One week later the eye had improved and most of the irritation was gone. The worker complained of episodes of headache and pain under or next to the eye. Reportedly the bag which the worker handled had a hole and was not properly sealed. No further information on the disposition of the case was reported.

Incident 5245-1

A pesticide incident occurred in 1997, when an applicator was applying fenamiphos and fertilizer to a golf course. The worker developed a rash with lesions on his arms three days later. However, follow-up on this case a day later found that this worker and others were exposed to poison oak while clearing out some brush. This case is unlikely due to the exposure to fenamiphos because the symptoms were inconsistent with exposure to an organophosphate.

Incident 7533-1

A pesticide incident occurred in 1998, when an applicator was applying fenamiphos to a golf course. The next day he had irritation around his right eye and red blotches on his foot. Cholinesterase tests taken on the day after his exposure were normal and somewhat elevated compared to his baseline levels. A tear in the man's boot may have been responsible for some exposure of his foot to the fenamiphos. No further information on the disposition of the case was reported.

Incident Not Yet Assigned a Number

A pesticide incident occurred in Hawaii in 1999, when workers were directed to apply fenamiphos without complying with required standards. One worker suffered acute poisoning (symptoms not specified) and was hospitalized. The employer has been charged with violations. Number of workers exposed, severity of the symptoms in the one worker who was poisoned, and presence of cholinesterase depression were not reported. No further information on the disposition of this case was reported.

(ii). Poison Control Center Data

1985-1992 Data

Fenamiphos had 16 occupationally-related incidents and 27 nonoccupational incidents reported between 1985 and 1992 due to this pesticide alone. Of the 16 occupationally-related incidents, 87.5% had symptoms thought to be related to their exposure and the same percentage were seen in a health care facility. Of those seen in a health care facility, 21.4% were hospitalized. These percentages were somewhat high compared to other cholinesterase-inhibiting insecticides, but based on a relatively small number of cases. None of the symptomatic cases resulted in life-threatening or fatal effects.

Among the 27 nonoccupational cases, 66.7% had symptoms thought to be related to their exposure and 63% were seen in a health care facility. Of those seen in a health care facility, 20% were hospitalized. The percentages reported health care received were higher than those for most other cholinesterase-inhibitors, but again, they are based on a relatively small number of cases. None of the cases were life-threatening or fatal.

1993-1996 Data

A total of 21 exposures to fenamiphos were reported to the Toxic Exposure Surveillance System of the American Association of Poison Control Centers. This is too few cases to permit meaningful comparisons with other pesticides. Six of the 21 cases were thought to have unrelated effects and most of the rest had at most minor effects, primarily nausea, vomiting, and abdominal pain. One occupational case was classified as having a moderate outcome and experienced slow heart rate, abdominal pain, diarrhea, vomiting, and muscle weakness. This case was hospitalized and treated in the intensive care unit. One other case was also hospitalized and seen in the intensive care unit but final medical outcome was determined to be minor. The effects in this latter case, abdominal pain, nausea and vomiting, persisted for two to three days.

Eleven of the 21 exposures were considered occupational and four were reported to be due to environmental exposures, suggesting exposure to residues (*e.g.*, spray from a hose leak to bystander or exposure to irrigation water). Two of the environmental cases had minor effects (nausea, vomiting, and/or abdominal pain) and two had potentially toxic effects (symptoms not reported in one case, but initially reported as sweating, miosis, and vomiting in the other).

(iii). California Data - 1982 through 1996

The California Pesticide Illness Surveillance Program reported 26 illnesses possibly, probably or definitely related to fenamiphos exposure or fenamiphos in combination with other pesticides. Of the 26 cases, fenamiphos was determined to be the primary pesticide associated with the illness in 10 cases. Five of the 10 cases involved pesticide handlers, including three applicators and two mixer/loaders. Two of the three applicators experienced a systemic illness from not wearing required protective equipment: one repairing an injection pump was hospitalized for two days and the other from hand watering granules into the soil on a golf course. A third applicator went to inspect a leak on a tractor rig when some of the material sprayed his eyes. A mixer/loader was loading fenamiphos through a closed system when a transfer hose broke. Although he was wearing a rain jacket and coveralls, the jacket was left unbuttoned. He was hospitalized for three days and lost nine days of work time. In a similar type of incident, another mixer loader was sprayed when the transfer hose came out of the tank and sprayed him resulting in diarrhea, headache, weakness, abdominal cramping, and nausea. Two other workers standing nearby, were also sprayed and experienced similar symptoms. Of the three remaining cases associated with fenamiphos, one was a drift exposure, and two resulted from exposure to irrigation water. In the first irrigation water case, an irrigator without required protective clothing placed his hand in the water and in the second case, a worker drank from an irrigation line. Four of the ten cases (three pesticide handlers and one exposed to drift) were categorized as probable or definite which indicates at least limited evidence that the health effects resulted from the exposures. In the remaining six cases the evidence indicated some contact with the pesticide before health effects developed, but it neither supported nor contradicted a causal relationship.

(iv). National Pesticide Telecommunications Network (NPTN)

On the list of the top 200 chemicals for which NPTN received calls from 1984-1991 inclusively, fenamiphos was not reported to be involved in human incidents.

(v). Conclusions

Relatively few incidents of illness have been reported due to fenamiphos. From cases in IDS and the California data it appears that equipment malfunction and failure to adhere to protective equipment requirements are significant factors leading to poisoning. Poison Control Center data are relatively sparse but suggest that fenamiphos poisonings are similar to other cholinesterase inhibitors in terms of severity of symptoms and requirements for health care.

(vi). Recommendations

Personal protective equipment requirements including protective eyewear should extend to transfer, repair, and maintenance activities.

5. Aggregate Exposure Risk Assessment

Aggregate risk is estimated by combining dietary (food and water) and nonoccupational exposures. Fenamiphos has no residential uses; however potential postapplication exposures to golfers (short-term) could occur following applications to golf course turf. Therefore, the aggregate risk estimates are based on the dietary exposure from food, nonoccupational postapplication exposure, and water. The estimates for the most highly exposed population subgroups and the general population as appropriate.

a. Acute Aggregate Exposure Risk Estimates

Acute aggregate risk estimates exceed the Agency's level of concern.

Acute aggregate risk estimates are derived using the combined dietary (food and water) exposure. Acute dietary food exposure has been highly refined using: probabilistic techniques (Monte Carlo); residue values derived from the USDA PDP and

FDA Surveillance Monitoring Program; distribution of residues or anticipated residues calculated from field trial data (only if PDP or FDA data not available); and incorporation of percent crop treated data (as supplied by BEAD in 1999).

Food exposure estimates are based on exposure at the 99.9th percentile. For the U.S. Population, the highest percent of the aPAD occupied is 27 and for the most highly exposed subpopulation, nursing infants less than one-year old, it is 68 percent of the aPAD. DWLOCs were calculated using these dietary (food) exposure estimates. Emerging policy (as presented at the TRAC meetings) concerning commodities having all nondetectable residues in monitoring programs dictates that another exposure analysis be conducted assuming zero residues present. If this assumption is made, then there is zero acute dietary exposure to fenamiphos.

Based on EFED Tier 1 and Tier 2 modeling for surface water (GENEEC and PRZM-EXAMS), the lowest of the maximal (day 0) EECs for fenamiphos in surface water is 105 ppb (range for four crops was 105 to 651 ppb). This conservative modeling estimate exceeds DWLOC for the U.S. Population (which is 30 ppb) and the DWLOC for nursing infants less than one-year old, which is 4 ppb.

For groundwater, high-quality monitoring data are available for the parent and the sulfoxide and sulfone degradates. Therefore, an acute risk estimate was calculated for fenamiphos, fenamiphos sulfoxide, and fenamiphos sulfone in groundwater that could be used for drinking. For children, 750% of the aPAD is occupied, and for adult males and females, 170% and 250% respectively. Adding acute dietary (food) risk estimates to these values would only result in further exceedence of the aPAD, although the contribution of food to the aggregate estimate is small in comparison to the groundwater contribution (approximately 10-fold less).

b. Short-Term Aggregate Exposure and Risk Estimates

Short-term aggregate risk estimates exceed the Agency's's level of concern. Aggregate risk assessments require that short-term nonoccupational exposures be aggregated with chronic dietary (food) and drinking exposures. The calculated MOEs from the nonoccupational exposure scenarios alone exceed the Agency's's level of concern (the short-term MOEs for postapplication dermal exposure of golfers from fenamiphos-treated golf course turf range from 49 (adolescent) to 78 (adults) from TTRs of five percent, both below 100).

HED anticipates that aggregating exposures from food and water would only result in a risk estimate that would further exceed the Agency's's level of concern. Thus, until nonoccupational postapplication short-term dermal exposure and risk estimates are mitigated to levels that do not exceed the Agency's's level of concern, aggregate short-term risk estimates exceed the Agency's's level of concern.

c. Chronic Aggregate Exposure and Risk Estimates

Chronic aggregate risk estimates exceed the Agency's level of concern.

Chronic aggregate risk estimates are derived using the combined dietary (food and water) exposure. Chronic dietary food exposure has been highly refined using anticipated residues based primarily on PDP and FDA monitoring data and percent crop treated data. Chronic dietary exposure from food alone does not exceed The Agency's level of concern. The percent of the cPAD occupied from chronic food exposure alone ranges from 4% for the U.S. Population to 14% for children 1-6 years old. The chronic DWLOC for the U.S. Population is 3 ppb and for children it is 1 ppb.

Based on EFED Tier 1 and Tier 2 modeling for surface water (GENEEC and PRZM-EXAMS), the lowest of the chronic (90 day) EECs for fenamiphos in surface water is 47 ppb (range for four crops was 47 to 329 ppb). This conservative modeling estimate exceeds the DWLOC for the U.S. Population (which is 3 ppb) and the DWLOC for children 1-6 years old which is 1 ppb.

For groundwater, high-quality monitoring data are available for the parent and the sulfoxide and sulfone degradates. Therefore, a chronic risk estimate was calculated for fenamiphos, fenamiphos sulfoxide, and fenamiphos sulfone in groundwater that could be used for drinking. For children, 1000% of the cPAD is occupied, and for both adult males and females, 300% was occupied. Adding chronic dietary (food) risk estimates to these values would only result in further exceedence of the aPAD, although the contribution of food to the aggregate estimate is small in comparison to the groundwater contribution.

6. Cumulative Risk Assessment

Cumulative risk will be addressed once OPP has finalized its' policies and procedures for conducting a cumulative risk assessment for organophosphates. This is an ongoing effort in OPP.

7. Risk Mitigation Used In Risk Assessments

Mitigation techniques have been implemented by the registrant to reduce the exposure and risk to workers using products containing fenamiphos (see introduction to this document). The occupational exposure has been determined using the mitigation techniques for the major use sites involved. A summary of the mitigation techniques are as follows:

- ❖ reduced acreage from HED's default assumptions; for example the default acreage for groundboom and tractor-drawn equipment are equal to 80 acres treated per day.

- ❖ reduced rates on apples, cherries, nectarines, peaches, grapes, citrus and pineapples;

- ❖ reduction in the amount of product which can be applied per season on apples, cherries, nectarines, peaches, grapes, citrus, kiwifruit and pineapples;

- ❖ reduction in the number of applications per season on apples, cherries, nectarines, peaches, citrus and kiwifruit;

- ❖ limits on the number of applications on grapes;

- ❖ extension of the interval between applications on apples,

cherries, nectarines, peaches, grapes, and citrus;

- ❖ addition of an application interval on grapes and kiwifruit;
- ❖ replacement of the broadcast applications with band applications on pineapples;
- ❖ canceled use of NEMACUR 15% granular product on citrus; and
- ❖ restrictions on applications to golf courses (to minimize runoff).

8. Data Requirements

The following mixer/loader/applicator data requirements were identified to support reregistration of fenamiphos:

- ❖ Guideline 231 - Estimation of Dermal Exposure at Outdoor Sites. Studies are required for handlers in double-layer body protection and chemical-resistant gloves and additional studies are required for handlers using engineering controls.
    - ▸ mixing/loading with granulars and emulsifiable concentrates.
    - ▸ broadcast and banding application of granulars.
    - ▸ groundboom application of emulsifiable concentrates.
    - ▸ soil injection application.

- Guideline 232 - Estimation of Inhalation Exposure at Outdoor Sites. Studies are required for handlers wearing respirators and additional studies are required for handlers using engineering controls.

    - mixing/loading with granulars and emulsifiable concentrates.
    - broadcast and banding application of granulars.
    - groundboom application of emulsifiable concentrates.
    - soil injection application.

Based on the use information and data available, the following postapplication exposure data are required to support the reregistration of fenamiphos:

- 132-1(a) Turf Transferable Residue (TTR) dissipation study for golf course turf,

- 132-1(b) Soil Residue Dissipation,

- 133-3 Dermal Exposure, and

- 133-4 Inhalation Exposure. This study is for the uses that may involve human contact with treated soil. These include: pre-transplant strawberries and asparagus, ornamental nonflowering plants, ornamental herbaceous plants, sod farm turf, ornamental woody shrubs and vines, and all nursery stock. Data are required using both the EC and granular formulations.

The Agency requires data and/or further clarification of the use patterns involving workers handling or working with or in the treated soil which may result in postapplication exposure. These uses are on strawberries, asparagus, ornamental nonflowering plants, ornamental herbaceous plants, sod farm turf, ornamental woody shrubs and vines, and all nursery stock. For these sites, the 48-hour REI will be required, until receipt and evaluation of the additional data. The Agency requires confirmation that the golf course use does not result in postapplication exposure as a result of handling treated grass clippings.

Table 10. Summary of Occupational Exposure Values for Fenamiphos[1]

Exposure Scenario (Scen. #)	Application Targets	Baseline Unit Dermal Exposure (mg/lb ai)	Baseline Unit Inhalation Exposure (mg/lb ai)	Max. Rate (lb ai/acre)[1]	Daily Max. Treated[1] (Acres)	Baseline Daily Dermal Exposure (mg/day)[2]	Baseline Daily Inhalation Exposure (mg/day)[2]	Baseline Daily Dermal Dose[3] (mg/kg/day)	Baseline Daily Inhalation Dose[3] (mg/kg/day)
Mixer/Loader Exposure and Dose Levels									
Loading Granulars (I)	Commercial and Industrial Turf, Golf Course Turf	0.0076	1.7×10^{-3}	10	50	3.8	0.85	0.054	0.012
	Pineapple			9	20	1.4	0.31	0.020	0.004
	Protea			9.75	5	0.37	0.08	0.005	0.001
	Leatherleaf Fern, Anthurium			10	5	0.38	0.09	0.005	0.001
	Ornamental Shade Trees, Ornamental Herbaceous Plants, Ornamental Woody Shrubs and Vines			10	10	0.76	0.17	0.011	0.002
	Iris, Lily, Narcissus			10	5	0.38	0.09	0.005	0.001
	Cabbage, Pepper, Chinese Cabbage, Okra, Brussels Sprouts			3	12	0.27	0.06	0.004	0.0009
	Peanuts			3	50	1.1	0.26	0.016	0.004
	Strawberries (Production and Nonbearing Nursery Stock), Eggplant			2	10	0.15	0.03	0.002	0.0004
	Strawberries (Production and Nonbearing Nursery Stock)			2.7	10	0.21	0.05	0.003	0.0007
	Garlic			4.5	10	0.34	0.08	0.005	0.001
	Ornamental Herbaceous Plants			10	5	0.38	0.09	0.005	0.001

Exposure Scenario (Scen. #)	Application Targets	Baseline Unit Dermal Exposure (mg/lb ai)	Baseline Unit Inhalation Exposure (mg/lb ai)	Max. Rate (lb ai/acre)$_1$	Daily Max. Treated[1] (Acres)	Baseline Daily Dermal Exposure (mg/day)[2]	Baseline Daily Inhalation Exposure (mg/day)[2]	Baseline Daily Dermal Dose[3] (mg/kg/day)	Baseline Daily Inhalation Dose[3] (mg/kg/day)
Mixing Liquid Formulations Groundboom Applications (II)	Cotton (in furrow)	2.9	1.2×10^{-3}	1.47	50	213	0.09	3.04	0.001
	Ornamental Herbaceous Plants			12	5	174	0.07	2.49	0.001
	Cotton (banding)			2.17	50	315	0.13	4.50	0.002
	Beets, Asparagus, Eggplant			2	10	58	0.02	0.83	0.0003
	Strawberry			2.7	10	78	0.03	1.11	0.0004
	Peanuts			2.47	50	358	0.15	5.11	0.002
	Apple, Cherry, Citrus, Nectarine, Peaches			7.5	40	870	0.36	12.4	0.005
	Grapes			6	40	696	0.29	9.94	0.004
	Raspberry			6	5	87	0.04	1.24	0.0006
	Tobacco			6	55	957	0.40	13.7	0.006
	Pineapple			9	20	522	0.22	7.46	0.003
	Leather Leaf Fern			9	5	131	0.05	1.87	0.0008
	Ornamental Woody Shrubs and Vines			10	5	145	0.06	2.07	0.0009
	Turf, Golf Course and Sod Farm Turf			10	40	1,160	0.48	16.6	0.007
	Banana [24(C)]			5	10	145	0.06	2.07	0.0009

Exposure Scenario (Scen. #)	Application Targets	Baseline Unit Dermal Exposure (mg/lb ai)	Baseline Unit Inhalation Exposure (mg/lb ai)	Max. Rate (lb ai/acre)$_1$	Daily Max. Treated[1] (Acres)	Baseline Daily Dermal Exposure (mg/day)[2]	Baseline Daily Inhalation Exposure (mg/day)[2]	Baseline Daily Dermal Dose[3] (mg/kg/day)	Baseline Daily Inhalation Dose[3] (mg/kg/day)
Mixing Liquid Formulations For Chemigation (III)	Pome/Stone/Citrus Fruits, Grapes, Kiwi, Pineapple	2.9	1.2×10^{-3}	3	80	696	0.29	9.9	0.004
	Banana [24 (c)]			4.5	10	131	0.05	1.9	0.0007
	Leather Leaf Fern			9	5	131	0.05	1.9	0.0008
	Ornamental Nonflowering Plants			12	20	696	0.29	9.9	0.004
Applicator Exposure and Dose Levels									
Groundboom Application (IV)	Cotton (in furrow)	0.015	7×10^{-4}	1.47	50	1.1	0.05	0.016	0.0007
	Ornamental Herbaceous Plants			12	5	0.9	0.04	0.013	0.0006
	Cotton (banding)			2.17	50	1.6	0.08	0.023	0.001
	Beets, Asparagus, Eggplant			2	10	0.3	0.01	0.004	0.0001
	Strawberry,			2.7	10	0.41	0.02	0.006	0.0003
	Peanuts			2.47	50	1.9	0.09	0.027	0.001
	Apple, Cherry, Citrus, Nectarine, Peaches			7.5	40	4.5	0.21	0.064	0.003
	Grapes			6	40	3.6	0.17	0.051	0.002
	Raspberry			6	5	0.45	0.021	0.006	0.0003
	Tobacco			6	55	4.95	0.23	0.071	0.003
	Pineapple			9	20	2.7	0.13	0.039	0.002

Exposure Scenario (Scen. #)	Application Targets	Baseline Unit Dermal Exposure (mg/lb ai)	Baseline Unit Inhalation Exposure (mg/lb ai)	Max. Rate (lb ai/acre)$_1$	Daily Max. Treated[1] (Acres)	Baseline Daily Dermal Exposure (mg/day)[2]	Baseline Daily Inhalation Exposure (mg/day)[2]	Baseline Daily Dermal Dose[3] (mg/kg/day)	Baseline Daily Inhalation Dose[3] (mg/kg/day)
Groundboom Application (IV) (con't)	Leather Leaf Fern	0.015	7×10^{-4}	9	5	0.68	0.032	0.010	0.0005
	Ornamental Woody Shrubs and Vines			10	5	0.75	0.035	0.011	0.0005
	Turf, Golf Course and Sod Farm Turf			10	40	6	0.28	0.086	0.004
	Banana [24(C)]			5	10	0.75	0.035	0.011	0.0005
Soil Injection (V)	Cotton	No Data	No Data	3	50	No data	No data	No data	No data
Tractor-Drawn Granular Application (VI)	Commercial and Industrial Turf, Golf Course Turf	0.01	1.2×10^{-3}	10	50	5	0.6	0.071	0.009
	Pineapple			9	20	1.8	0.216	0.026	0.003
	Protea			9.75	5	0.49	0.059	0.007	0.0008
	Leatherleaf Fern, Anthurium			10	5	0.5	0.06	0.007	0.0009
	Ornamental Shade Trees, Ornamental Herbaceous Plants, Ornamental Woody Shrubs and Vines			10	10	1	0.12	0.014	0.002
	Iris, Lily, Narcissus			10	5	0.5	0.06	0.007	0.0009
	Cabbage, Pepper, Chinese Cabbage, Okra, Brussels Sprouts			0.17 lb/1000 row (3.0 lb/acre on 30" rows)	12	0.36	0.043	0.005	0.0006
	Peanuts				50	1.5	0.18	0.021	0.0026

Exposure Scenario (Scen. #)	Application Targets	Baseline Unit Dermal Exposure (mg/lb ai)	Baseline Unit Inhalation Exposure (mg/lb ai)	Max. Rate (lb ai/acre)[1]	Daily Max. Treated[1] (Acres)	Baseline Daily Dermal Exposure (mg/day)[2]	Baseline Daily Inhalation Exposure (mg/day)[2]	Baseline Daily Dermal Dose[3] (mg/kg/day)	Baseline Daily Inhalation Dose[3] (mg/kg/day)
Tractor-Drawn Granular Application (cont.) (VI)	Strawberries (Production and Nonbearing Nursery Stock), Eggplant	0.01	1.2×10^{-3}	2	10	0.20	0.024	0.003	0.0003
	Cabbage, Brussels Sprouts			3	12	0.36	0.043	0.005	0.0006
	Strawberries (Production and Nonbearing Nursery Stock)			2.7	10	0.27	0.032	0.004	0.0005
	Garlic			4.5	10	0.45	0.054	0.006	0.0008
	Ornamental Herbaceous Plants			10	5	0.50	0.060	0.007	0.0009

1Crop and use data were provided by the registrant as proposed risk mitigation.
2Daily Exposure (mg/day) = Exposure (mg/lb ai) * Max. Appl. Rate (lb ai/acre) * Max. Treated.
3Daily Dose (mg/kg/day) = Daily Exposure (mg/day)/70 kg.

Baseline Unit Exposure is based on workers wearing long sleeve shirts and long pants, and no gloves.

Table 11. Exposure Scenario Descriptions for Fenamiphos

Exposure Scenario (Scen. #)	Data Source	Standard Assumptions[1]	Comments[2]
Mixer/Loader Exposure Levels			
Loading Granulars (I)	PHED V1.1	Use data supplied by the registrant	**Baseline:** "Best Available" grades: Dermal and inhalation acceptable grades; hand all grades. Dermal = 29 to 36 replicates; Hands = 10 replicates; Inhalation = 58 replicates. Low confidence in dermal and high confidence for inhalation data. No protection factors (PFs) were necessary. **PPE:** "Best Available" grades: Hands and dermal acceptable grades. Hands = 45 replicates; Dermal = 29 to 36 replicates. High confidence in dermal data. A 50 percent PF was used for the addition of coveralls.
Mixing Liquid Formulations for Groundboom Applications (II)	PHED V1.1	Use data supplied by the registrant	**Baseline:** "Best Available" grades: Dermal, hands, and inhalation acceptable grades. Dermal = 25 to 122 replicates; Hands = 53 replicates; Inhalation = 85 replicates. High confidence in dermal and inhalation data. No protection factors (PFs) were necessary. **PPE:** "Best Available" grades: Hands and dermal acceptable grades. Hands = 59 replicates; Dermal = 25 to 122 replicates. High confidence in dermal data. A 50 percent PF was used for the addition of coveralls. **ENGINEERING CONTROLS:** "Best Available" grades: Dermal, hands, and inhalation acceptable grades. Hands = 59 replicates; Dermal = 25 to 122 replicates; Inhalation = 27 replicates. High confidence in dermal and inhalation data. No PFs were necessary. Note: Worker wearing chemical resistant gloves, data are not available for the no glove scenario.
Mixing Liquid Formulations for Chemigation (III)	PHED V1.1	Use data supplied by the registrant	
Applicator Exposure Levels			
Groundboom Application (IV)	PHED V1.1	Use data supplied by the registrant	**Baseline:** "Best Available" grades: Dermal, hands, and inhalation acceptable grades. Dermal = 32 to 42 replicates; Hands = 29 replicates; Inhalation = 22 replicates. High confidence in dermal and inhalation data. No protection factors (PFs) were necessary. **PPE:** "Best Available" grades: Dermal acceptable grades; hands grade A, B, C. Hands = 21 replicates; Dermal = 32 to 42 replicates. Medium confidence in dermal data. A 50 percent PF was used for the addition of coveralls. **ENGINEERING CONTROLS:** "Best Available" grades: Dermal and hands grades A, B, C; inhalation acceptable grades. Hands = 16 replicates; Dermal = 20 to 31 replicates; Inhalation = 16 replicates. Medium confidence in dermal and high confidence for inhalation data. No PFs were necessary.
Soil Injection (V)	No Data	No Data	No data

Exposure Scenario (Scen. #)	Data Source	Standard Assumptions[1]	Comments[2]
Tractor-Drawn Granular Application (VI)	PHED V1.1	Use data supplied by the registrant	**Baseline:** "Best Available" grades: Dermal, hands, and inhalation acceptable grades. Dermal = 4 to 5 replicates; Hands = 5 replicates; Inhalation = 5 replicates. Low confidence in dermal and inhalation data. No protection factors (PFs) were necessary. **PPE:** "Best Available" grades: Dermal and hands acceptable grades. Hands = 5 replicates; Dermal = 4 to 5 replicates. Low confidence in dermal data. A 50 percent PF was used for the addition of coveralls and a 90 percent PF was used for the addition of chemical resistant gloves. **ENGINEERING CONTROLS:** "Best Available" grades: Dermal, hands, and inhalation acceptable grades. Hands = 24 replicates; Dermal = 24 to 25 replicates; Inhalation = 20 replicates. High confidence in dermal and inhalation data. No PFs were necessary.

[1]Standard Assumptions based on the registrant's risk mitigation response dated August 14, 1996.

[2]"Best Available" grades are defined by Exposure Scientific Advisory Council (SAC) Standard Operating Procedure for meeting Subdivision U Guidelines. Best available grades are assigned as follows: matrices with grades A and B data and a minimum of 15 replicates; if not available, then grades A, B, and C data and a minimum of 15 replicates; if not available, then all data regardless of the quality and number of replicates. Data confidence are assigned as follows:
High=grades A and B and 15 or more replicates per body part Medium= grades A, B, and C and 15 or more replicates per body part
Low= grades A, B, C, D, and E or any combination of grades with less than 15 replicates

Table 12. Summary of Dermal Occupational Baseline Margins of Exposure (MOEs) and Risk Mitigation for Fenamiphos[1]

Exposure Scenario (Scen. #)	Application Targets	Baseline Dermal MOEs[2]	Risk Mitigation Measures							
			Additional PPE[3]				Engineering Controls[4]			
			Unit Dermal Exposure (mg/lb ai)	Daily Dermal Exposure[5] (mg/day)	Daily Dermal Dose[6] (mg/kg/day)	MOE[2]	Unit Dermal Exposure (mg/lb ai)	Daily Dermal Exposure[5] (mg/day)	Daily Dermal Dose[6] (mg/kg/day)	MOE[2]
Mixer/Loader Exposure and Dose Levels										
Loading Granulars (I)	Commercial and Industrial Turf, Golf Course Turf	46	0.003	1.5	0.021	119	NA	NA	NA	NA
	Pineapple	125		NA	NA	NA	NA	NA	NA	NA
	Protea	500		NA	NA	NA	NA	NA	NA	NA
	Leatherleaf Fern, Anthurium	500		NA	NA	NA	NA	NA	NA	NA
	Ornamental Shade Trees, Ornamental Herbaceous Plants, Ornamental Woody Shrubs and Vines	227		NA	NA	NA	NA	NA	NA	NA
	Iris, Lily, Narcissus,	500		NA	NA	NA	NA	NA	NA	NA
	Cabbage, Pepper, Chinese Cabbage, Okra, Brussels Sprouts	625		NA	NA	NA	NA	NA	NA	NA
	Peanuts	156		NA	NA	NA	NA	NA	NA	NA

Exposure Scenario (Scen. #)	Application Targets	Baseline Dermal MOEs[2]	Risk Mitigation Measures							
			Additional PPE[3]				Engineering Controls[4]			
			Unit Dermal Exposure (mg/lb ai)	Daily Dermal Exposure[5] (mg/day)	Daily Dermal Dose[6] (mg/kg/day)	MOE[2]	Unit Dermal Exposure (mg/lb ai)	Daily Dermal Exposure[5] (mg/day)	Daily Dermal Dose[6] (mg/kg/day)	MOE[2]
Loading Granules (I) (cont.)	Strawberries (Production and Nonbearing Nursery Stock), Eggplant	1,250	0.003	NA	NA	NA	NA	NA	NA	NA
	Cabbage, Brussels Sprouts	625		NA	NA	NA	NA	NA	NA	NA
	Strawberries (Production and Nonbearing Nursery Stock)	833		NA	NA	NA	NA	NA	NA	NA
	Garlic	500		NA	NA	NA	NA	NA	NA	NA
	Ornamental Herbaceous Plants	500		NA	NA	NA	NA	NA	NA	NA
Mixing Liquid Formulations for Groundboom Applications (II)	Cotton (in furrow)	<1	0.025	1.84	0.026	96	0.009 (gloves)	0.66	0.009	278
	Ornamental Herbaceous Plants	1		1.5	0.021	119		NA	NA	NA
	Cotton (banding)	<1		2.71	0.039	64		0.98	0.014	179
	Beets, Asparagus, Eggplants	3		0.50	0.007	357		NA	NA	NA
	Strawberry	2		0.68	0.010	250		NA	NA	NA
	Peanuts	<1		3.1	0.044	57		1.1	0.016	156

Exposure Scenario (Scen. #)	Application Targets	Baseline Dermal MOEs[2]	Risk Mitigation Measures							
			Additional PPE[3]				Engineering Controls[4]			
			Unit Dermal Exposure (mg/lb ai)	Daily Dermal Exposure[5] (mg/day)	Daily Dermal Dose[6] (mg/kg/day)	MOE[2]	Unit Dermal Exposure (mg/lb ai)	Daily Dermal Exposure[5] (mg/day)	Daily Dermal Dose[6] (mg/kg/day)	MOE[2]
Mixing Liquids for Groundboom Applications (II) (cont.)	Apple, Cherry, Citrus, Nectarine, Peaches	<1	0.025	7.5	0.11	23	0.009 (gloves)	2.7	0.039	64
	Grapes	<1		6.0	0.086	29		2.2	0.031	81
	Raspberry	2		0.75	0.011	227		NA	NA	NA
	Tobacco	<1		8.3	0.12	21		3.0	0.042	60
	Pineapple	<1		4.5	0.064	39		1.6	0.023	109
	Leather Leaf Fern	1		1.1	0.016	156		NA	NA	NA
	Ornamental Woody Shrubs and Vines	1		1.3	0.019	132		NA	NA	NA
	Turf, Golf Course and sod farm Turf	<1		10	0.14	18		3.6	0.051	49
	Banana [24(C)]	1		1.3	0.019	132		NA	NA	NA

Exposure Scenario (Scen. #)	Application Targets	Baseline Dermal MOEs[2]	Risk Mitigation Measures							
			Additional PPE[3]				Engineering Controls[4]			
			Unit Dermal Exposure (mg/lb ai)	Daily Dermal Exposure[5] (mg/day)	Daily Dermal Dose[6] (mg/kg/day)	MOE[2]	Unit Dermal Exposure (mg/lb ai)	Daily Dermal Exposure[5] (mg/day)	Daily Dermal Dose[6] (mg/kg/day)	MOE[2]
Mixing Liquid Formulations For Chemigation (III)	Pome/Stone/Citrus Fruits, Grapes, Kiwi, Pineapple	<1	0.025	6.0	0.086	29	0.009 (gloves)	2.2	0.031	80
	Banana [24(C)]	1		1.1	0.016	156		NA	NA	NA
	Leather Leaf Fern	1		1.1	0.016	156		NA	NA	NA
	Ornamental Nonflowering Plants	<1		6.0	0.086	29		2.2	0.031	81
Applicator Exposure and Dose Levels										
Groundboom Application (IV)	Cotton (in furrow)	156	0.01	NA	NA	NA	0.0067	NA	NA	NA
	Ornamental Herbaceous Plants	192		NA	NA	NA		NA	NA	NA
	Cotton (banding)	109		NA	NA	NA		NA	NA	NA
	Beets, Asparagus, Eggplants	625		NA	NA	NA		NA	NA	NA
	Strawberry	417		NA	NA	NA		NA	NA	NA
	Peanuts	93		1.2	0.017	147		NA	NA	NA
	Apple, Cherry, Citrus, Nectarine, Peaches	39		3.0	0.043	58		2.0	0.029	86

Exposure Scenario (Scen. #)	Application Targets	Baseline Dermal MOEs[2]	Risk Mitigation Measures							
			Additional PPE[3]				Engineering Controls[4]			
			Unit Dermal Exposure (mg/lb ai)	Daily Dermal Exposure[5] (mg/day)	Daily Dermal Dose[6] (mg/kg/day)	MOE[2]	Unit Dermal Exposure (mg/lb ai)	Daily Dermal Exposure[5] (mg/day)	Daily Dermal Dose[6] (mg/kg/day)	MOE[2]
Groundboom Application (IV) (con't)	Grapes	49	0.01	2.4	0.034	74	0.0067	1.6	0.023	109
	Raspberry	417		NA	NA	NA		NA	NA	NA
	Tobacco	35		3.3	0.047	53		2.2	0.031	81
	Pineapple	64		1.8	0.026	96		1.2	0.017	147
	Leather Leaf Fern	250		NA	NA	NA		NA	NA	NA
	Ornamental Woody Shrubs and Vines	227		NA	NA	NA		NA	NA	NA
	Turf, Golf Course and sod farm Turf	29		4.0	0.057	44		2.7	0.039	64
	Banana [24(C)]	227		NA	NA	NA		NA	NA	NA
Soil Injection (V)	Cotton	No data	No data	No data	No data	No data	No data	No data	No data	No data

Exposure Scenario (Scen. #)	Application Targets	Baseline Dermal MOEs[2]	Risk Mitigation Measures							
			Additional PPE[3]				Engineering Controls[4]			
			Unit Dermal Exposure (mg/lb ai)	Daily Dermal Exposure[5] (mg/day)	Daily Dermal Dose[6] (mg/kg/day)	MOE[2]	Unit Dermal Exposure (mg/lb ai)	Daily Dermal Exposure[5] (mg/day)	Daily Dermal Dose[6] (mg/kg/day)	MOE[2]
Tractor-Drawn Granular Application (VI)	Commercial and Industrial Turf, Golf Course Turf	35	0.0038	1.9	0.027	93	0.0022	1.1	0.016	156
	Pineapple	96		0.68	0.0097	258		NA	NA	NA
	Protea	357		NA	NA	NA		NA	NA	NA
	Leatherleaf Fern, Anthurium	357		NA	NA	NA		NA	NA	NA
	Ornamental Shade Trees, Ornamental Herbaceous Plants, Ornamental Woody Shrubs and Vines	179		NA	NA	NA		NA	NA	NA
	Iris, Lily, Narcissus,	357		NA	NA	NA		NA	NA	NA
	Cabbage, Pepper, Chinese Cabbage, Okra, Brussels Sprouts	500		NA	NA	NA		NA	NA	NA
	Peanuts	119		NA	NA	NA		NA	NA	NA
	Strawberries (Production and Nonbearing Nursery Stock), Eggplant	833		NA	NA	NA		NA	NA	NA

Exposure Scenario (Scen. #)	Application Targets	Baseline Dermal MOEs[2]	Risk Mitigation Measures							
			Additional PPE[3]				Engineering Controls[4]			
			Unit Dermal Exposure (mg/lb ai)	Daily Dermal Exposure[5] (mg/day)	Daily Dermal Dose[6] (mg/kg/day)	MOE[2]	Unit Dermal Exposure (mg/lb ai)	Daily Dermal Exposure[5] (mg/day)	Daily Dermal Dose[6] (mg/kg/day)	MOE[2]
Tractor-Drawn Granular Application (VI)	Cabbage, Brussels Sprouts	500	0.0038	NA	NA	NA	0.0022	NA	NA	NA
	Strawberries (Production and Nonbearing Nursery Stock)	625		NA	NA	NA		NA	NA	NA
	Garlic	417		NA	NA	NA		NA	NA	NA
	Ornamental Herbaceous Plants	357		NA	NA	NA		NA	NA	NA

NA. Not applicable, previous MOE >100.

[1]Crop and use data were provided by the registrant as proposed risk mitigation.

[2]MOE values calculated using the following equation: MOE = NOAEL (mg/kg/day)/dermal dose (mg/kg/day); where dermal NOAEL = 2.5 mg/kg/day (see Dose Response Assessment for details).

[3]PPE = coveralls over single layer clothing and chemical resistant gloves.

[4]Engineering Controls = single layer clothing and no gloves (except where noted chemical resistant gloves -- because the no glove scenario is not available) and closed mixing systems and enclosed cab tractors.

[5]Daily Exposure (mg/day) = Exposure (mg/lb ai) * Max. Appl. Rate (lb ai/acre) * Max. Treated.

[6]Daily Dose (mg/kg/day) = Daily Exposure (mg/day)/70 kg.

Table 13. Summary of Inhalation Occupational Baseline Margins of Exposure (MOEs) and Risk Mitigation for Fenamiphos

Exposure Scenario (Scen. #)	Application Targets	Baseline Inhalation MOEs[2]	Risk Mitigation Measures				
			Additional PPE[3]	Engineering Controls[4]			
			Inhalation MOE[7]	Unit Inhalation Exposure (mg/lb ai)	Daily Inhalation Exposure[5] (mg/day)	Daily Inhalation Dose[6] (mg/kg/day)	MOE[2]
Mixer/Loader Exposure and Dose Levels							
Loading Granulars (I)	Commercial and Industrial Turf, Golf Course Turf	5	25	3.4×10^{-5}	0.017	0.0002	305
	Pineapple	15	75		0.006	0.00009	678
	Protea	61	305		NA	NA	NA
	Leatherleaf Fern, Anthurium	61	305		NA	NA	NA
	Ornamental Shade Trees, Ornamental Herbaceous Plants, Ornamental Woody Shrubs and Vines	31	155		NA	NA	NA
	Iris, Lily, Narcissus,	61	305		NA	NA	NA
	Cabbage, Pepper, Chinese Cabbage, Okra, Brussels Sprouts	68	340		NA	NA	NA
	Peanuts	15	75		0.005	0.00007	871

Exposure Scenario (Scen. #)	Application Targets	Baseline Inhalation MOEs[2]	Risk Mitigation Measures				
			Additional PPE[3]	Engineering Controls[4]			
			Inhalation MOE[7]	Unit Inhalation Exposure (mg/lb ai)	Daily Inhalation Exposure[5] (mg/day)	Daily Inhalation Dose[6] (mg/kg/day)	MOE[2]
Loading Granules (I) (cont.)	Strawberries (Production and Nonbearing Nursery Stock), Eggplant	153	NA	3.4×10^{-5}	NA	NA	NA
	Cabbage, Brussels Sprouts	68	340		NA	NA	NA
	Strawberries (Production and Nonbearing Nursery Stock)	87	435		NA	NA	NA
	Garlic	61	305		NA	NA	NA
	Ornamental Herbaceous Plants	61	305		NA	NA	NA
Mixing Liquid Formulations for Groundboom Applications (II)	Cotton (in furrow)	61	305	8.0×10^{-5}	NA	NA	NA
	Ornamental Herbaceous Plants	61	305		NA	NA	NA
	Cotton (banding)	31	155		NA	NA	NA
	Beets, Asparagus, Eggplants	203	NA		NA	NA	NA
	Strawberry	153	NA		NA	NA	NA

Exposure Scenario (Scen. #)	Application Targets	Baseline Inhalation MOEs[2]	Risk Mitigation Measures				
			Additional PPE[3]	Engineering Controls[4]			
			Inhalation MOE[7]	Unit Inhalation Exposure (mg/lb ai)	Daily Inhalation Exposure[5] (mg/day)	Daily Inhalation Dose[6] (mg/kg/day)	MOE[2]
Mixing Liquid Formulations for Groundboom Applications (II) (cont.)	Peanuts	31	155	8.0×10^{-5}	NA	NA	NA
	Apple, Cherry, Citrus, Nectarine, Peaches	12	60		0.02	0.0003	203
	Grapes	15	75		0.02	0.0003	203
	Raspberry	102	NA		NA	NA	NA
	Tobacco	10	50		0.03	0.0004	153
	Pineapple	20	100		NA	NA	NA
	Leather Leaf Fern	76	380		NA	NA	NA
	Ornamental Woody Shrubs and Vines	68	340		NA	NA	NA
	Turf, Golf Course and sod farm Turf	9	45		0.03	0.0004	153
	Banana [24(C)]	68	340		NA	NA	NA

Exposure Scenario (Scen. #)	Application Targets	Baseline Inhalation MOEs[2]	Risk Mitigation Measures				
			Additional PPE[3]	Engineering Controls[4]			
			Inhalation MOE[7]	Unit Inhalation Exposure (mg/lb ai)	Daily Inhalation Exposure[5] (mg/day)	Daily Inhalation Dose[6] (mg/kg/day)	MOE[2]
Mixing Liquid Formulations For Chemigation (III)	Pome/Stone/Citrus Fruits, Grapes, Kiwi, Pineapple	15	75	8.0×10^{-5}	0.02	0.0003	203
	Banana [24(C)]	87	435		NA	NA	NA
	Leather Leaf Fern	76	380		NA	NA	NA
	Ornamental Nonflowering Plants	15	75		0.02	0.0003	203
Applicator Exposure and Dose Levels							
Groundboom Application (IV)	Cotton (in furrow)	87	435	4.3×10^{-5}	NA	NA	NA
	Ornamental Herbaceous Plants	102	NA		NA	NA	NA
	Cotton (banding)	61	305		NA	NA	NA
	Beets, Asparagus, Eggplants	610	NA		NA	NA	NA
	Strawberry	203	NA		NA	NA	NA
	Peanuts	61	305		NA	NA	NA

Exposure Scenario (Scen. #)	Application Targets	Baseline Inhalation MOEs[2]	Risk Mitigation Measures				
			Additional PPE[3]	Engineering Controls[4]			
			Inhalation MOE[7]	Unit Inhalation Exposure (mg/lb ai)	Daily Inhalation Exposure[5] (mg/day)	Daily Inhalation Dose[6] (mg/kg/day)	MOE[2]
Groundboom Application (IV) (cont.)	Apple, Cherry, Citrus, Nectarine, Peaches	20	100	4.3×10^{-5}	NA	NA	NA
	Grapes	31	155		NA	NA	NA
	Raspberry	203	NA		NA	NA	NA
	Tobacco	20	100		NA	NA	NA
	Pineapple	31	155		NA	NA	NA
	Leather Leaf Fern	122	NA		NA	NA	NA
	Ornamental Woody Shrubs and Vines	122	NA		NA	NA	NA
	Turf, Golf Course and sod farm Turf	15	75		0.017	0.0002	305
	Banana [24(C)]	122	NA		NA	NA	NA
Soil Injection (V)	Cotton	No data	No data	No data	No data	No data	No data

Exposure Scenario (Scen. #)	Application Targets	Baseline Inhalation MOEs[2]	Risk Mitigation Measures				
			Additional PPE[3]	Engineering Controls[4]			
			Inhalation MOE[7]	Unit Inhalation Exposure (mg/lb ai)	Daily Inhalation Exposure[5] (mg/day)	Daily Inhalation Dose[6] (mg/kg/day)	MOE[2]
Tractor- Drawn Granular Application (VI)	Commercial and Industrial Turf, Golf Course Turf	7	35	1.4×10^{-4}	0.07	0.001	61
	Pineapple	20	100		NA	NA	NA
	Protea	76	380		NA	NA	NA
	Leatherleaf Fern, Anthurium	68	340		NA	NA	NA
	Ornamental Shade Trees, Ornamental Herbaceous Plants, Ornamental Woody Shrubs and Vines	31	155		NA	NA	NA
	Iris, Lily, Narcissus,	68	340		NA	NA	NA
	Cabbage, Pepper, Chinese Cabbage, Okra, Brussels Sprouts	102	NA		NA	NA	NA
	Peanuts	23	115		NA	NA	NA
	Strawberries (Production and Nonbearing Nursery Stock), Eggplant	203	NA		NA	NA	NA
	Cabbage, Brussels Sprouts	102	NA		NA	NA	NA
	Strawberries (Production and Nonbearing Nursery Stock)	122	NA		NA	NA	NA

Exposure Scenario (Scen. #)	Application Targets	Baseline Inhalation MOEs[2]	Risk Mitigation Measures				
			Additional PPE[3]	Engineering Controls[4]			
			Inhalation MOE[7]	Unit Inhalation Exposure (mg/lb ai)	Daily Inhalation Exposure[5] (mg/day)	Daily Inhalation Dose[6] (mg/kg/day)	MOE[2]
Tractor-Drawn Granular Application (VI)(cont.)	Garlic	76	380	1.4×10^{-4}	NA	NA	NA
	Ornamental Herbaceous Plants	68	340		NA	NA	NA

NA. Not applicable, previous MOE >100.

[1]Crop and use data were provided by the registrant as proposed risk mitigation.

[2]MOE values calculated using the following equation: MOE = NOAEL (mg/kg/day)/inhalation dose (mg/kg/day); where NOAEL = 0.061 mg/kg/day (see Dose Response Assessment for details).

[3]PPE = dust/mist respirator applied to the baseline MOE. (Decreases the baseline unit exposure by 80%, if and only if, the worker has achieved a protective seal. This is accomplished by the worker being medically qualified to wear the specific respirator, fit tested to ensure a protective seal was achieved, and he/she has had the appropriate training to maintain the respirator in good condition in accordance with the American National Standards Institute (ANSI) and or OSHA 29CFR 1910.34)

[4]Engineering Controls = closed mixing systems and enclosed cab tractors, no respirators.

[5]Daily Exposure (mg/day) = Exposure (mg/lb ai) * Max. Appl. Rate (lb ai/acre) * Max. Treated.

[6]Daily Dose (mg/kg/day) = Daily Exposure (mg/day)/70 kg.

[7]Dust/Mist Respirator, 5-Fold Protection Factor Applied to Baseline MOE

Table 14. Summary of Occupational (Separate Dermal and Inhalation)

Exposure Scenario[1]	DERMAL MOES[2]			INHALATION MOES[2]		
	Baseline (long sleeved shirt and long pants, no gloves)	With Additional Layer of Clothing and Gloves[3]	With Engineering Controls[4]	Baseline	With Dust/Mist Respirator (5-fold protection factor applied to baseline MOE)[3]	With Engineering Controls[4]
Mixer/Loader Liquids (Supporting Groundboom Application)	<1 - *apples, cherries, citrus, nectarines, peaches, grapes, tobacco, & turf*	23 - *apples, cherries, citrus, nectarines, & peaches* 18 - *grapes* 21- *tobacco* 18 - *turf*	64 - *apples, cherries, citrus, nectarines, & peaches* 49 - *grapes* 60 - *tobacco* 49 - *turf*	12 - *apples, cherries, citrus, nectarines, & peaches* 15 -*grapes* 10 - *tobacco* 9 - *turf*	60 - *apples, cherries, citrus, nectarines, & peaches* 75 - *grapes* 50 - *tobacco* 45 - *turf*	203 - *apples, cherries, citrus, nectarines, & peaches* 203 - *grapes* 153 - *tobacco* 153 - *turf*
Mixer/Loader Liquids (Supporting Chemigation Application)	<1 - *pome/stone/ citrus fruits, grapes, kiwi, pineapple, & ornamentals*	29 - *pome/stone/ citrus fruits, grapes, kiwi, pineapple, & ornamentals*	80 - *pome/stone/ citrus fruits, grapes, kiwi, & pineapple* 81- *ornamentals*	15 - *fruits, ornamentals*	75	203
Applicator Using Groundboom Application	39 - *apples, cherries, citrus, nectarines, & peaches* 35 - *tobacco* 29 - *turf*	58 -apples, cherries, citrus, nectarines, & peaches 53 - *tobacco* 44 - *turf*	86 -*apples, cherries, citrus, nectarines, & peaches* 81- *tobacco* 64 - *turf*	20 - *apples, cherries, citrus, nectarines, & peaches* 20 - *tobacco* 15 - *turf*	100 - *apples, cherries, citrus, nectarines, & peaches* 100 - *tobacco* 75 - *turf*	NA NA 305 - *turf*
Applicator Using Tractor-Drawn Granular(10G) Application	35 - *turf*	93	156	7 - *turf*	35	61

Notes for Table 14:

Dermal:

NA. Not applicable, previous MOE >100.

[1]Crop and use data were provided by the Registrant as proposed risk mitigation.
Daily Exposure (mg/day) = Exposure (mg/lb ai) * Max. Appl. Rate (lb ai/acre) * Max. Treated.
Daily Dose (mg/kg/day) = Daily Exposure (mg/day)/70 kg.

[2]MOE values calculated using the following equation: MOE = NOAEL (mg/kg/day)/dermal dose (mg/kg/day);
where dermal NOAEL = 2.5 mg/kg/day (see Dose Response Assessment for details).

[3]PPE = coveralls over single layer clothing and chemical resistant gloves.

[4]Engineering Controls = single layer clothing and no gloves (except where noted chemical resistant gloves
-- because the no glove scenario is not available) and closed mixing systems and enclosed cab tractors.

Inhalation:

NA. Not applicable, previous MOE >100.

[1]Crop and use data were provided by the Registrant as proposed risk mitigation.
Daily Exposure (mg/day) = Exposure (mg/lb ai) * Max. Appl. Rate (lb ai/acre) * Max. Treated.
Daily Dose (mg/kg/day) = Daily Exposure (mg/day)/70 kg.

[2]MOE values calculated using the following equation: MOE = NOAEL (mg/kg/day)/inhalation dose (mg/kg/day);
where NOAEL = 0.061 mg/kg/day (see Dose Response Assessment for details).

[3]PPE = dust/mist respirator applied to the baseline MOE (Decreases the baseline unit exposure by 80%, if and only if,
the worker has achieved a protective seal. This is accomplished by the worker being medically qualified to wear the specific respirator, fit tested to ensure a protective seal was achieved, and he/she has had the appropriate training to maintain the respirator in good condition in accordance with the American National Standards Institute (ANSI) and or OSHA 29CFR 1910.34) .

[4]Engineering Controls = closed mixing systems and enclosed cab tractors, no respirators.

Table 15. Occupational (Dermal + Inhalation) Aggregate MOEs (MOE aggregate = " Reciprocal Equation")

Application Targets (commodities)	Baseline			PPE			Engineering Controls		
	Dermal MOE	Inhalation MOE	Total (Aggregate) MOE	Dermal MOE	Inhalation MOE	Total (Aggregate) MOE	Dermal MOE	Inhalation MOE	Total (Aggregate) MOE
Scenario (I): Loading Granulars									
Commercial and Industrial Turf, Golf Course Turf	46	5.1	4.6	119	25	21	2059	305	266
Pineapple	125	15	14	324	75	61	5719	678	606
Protea	500	61	54	1197	305	243	21116	2576	2296
Leatherleaf Fern, Anthurium	500	61	54	1167	305	242	20588	2512	2239
Ornamental Shade Trees, Ornamental Herbaceous Plants, Ornamental Woody Shrubs and Vines	227	31	27	583	155	122	10294	1256	1119
Iris, Lily, Narcissus	500	61	54	1167	305	242	20588	2512	2239
Cabbage, Pepper, Chinese Cabbage, Okra, Brussels Sprouts	625	68	61	1620	340	281	28595	3489	3109
Peanuts	156	15	14	389	75	63	6863	871	773
Strawberries (Production and Nonbearing Nursery Stock), Eggplant	1250	153	136	2917	763	604	51471	6279	5597
Cabbage, Brussels Sprouts	625	68	61	1620	340	281	28595	3489	3109
Strawberries (Production and Nonbearing Nursery Stock)	833	87	79	2160	435	362	38126	4651	4146
Garlic	500	61	54	1296	305	247	22876	2791	2487
Ornamental Herbaceous Plants	500	61	54	1167	305	242	20588	2512	2239
Scenario (II): Mixing Liquid Formulations for Groundboom Applications									
Cotton (in furrow)	0.82	61	0.81	96	305	73	278	726	201
Ornamental Herbaceous Plants	1.00	61	0.99	119	305	86	324	890	238
Cotton (banding)	0.56	31	0.55	64	155	45	179	492	131
Beets, Asparagus, eggplant	3.01	203	2.97	357	1017	264	972	2669	713
Strawberry	2.25	153	2.22	250	763	188	720	1977	528
Peanuts	0.49	31	0.48	57	155	42	156	432	115
Apple, Cherry, Citrus, Nectarine, Peaches	0.20	12	0.20	23	60	17	64	203	49
Grapes	0.25	15	0.25	29	75	21	81	203	58
Raspberry	2.02	102	1.98	227	508	157	648	1779	475
Tobacco	0.18	10	0.18	21	50	15	60	153	43
Pineapple	0.34	20	0.33	39	100	28	109	297	80
Leather Leaf Fern	1.34	76	1.31	156	380	110	432	1186	317
Ornamental Woody Shrubs and Vines	1.21	68	1.19	132	340	95	389	1068	285

Application Targets (commodities)	Baseline			PPE			Engineering Controls		
	Dermal MOE	Inhalation MOE	Total (Aggregate) MOE	Dermal MOE	Inhalation MOE	Total (Aggregate) MOE	Dermal MOE	Inhalation MOE	Total (Aggregate) MOE
Turf, Golf Course and Sod Farm Turf	0.15	9	0.15	18	45	13	49	153	37
Banana [24(C)]	1.21	68	1.19	132	340	95	389	1068	285
Scenario (III): Mixing Liquid Formulations For Chemigation									
Pome/Stone/Citrus Fruits, Grapes, Kiwi, Pineapple	0.25	15	0.25	29	75	21	80	203	57
Banana [24 (c)]	1.32	87	1.30	156	435	115	432	1186	317
Leather Leaf Fern	1.32	76	1.29	156	380	110	432	1186	317
Ornamental Non-Flowering Plants	0.25	15	0.25	29	75	21	81	203	58
Scenario (IV): Groundboom Application									
Cotton (in furrow)	156	87	56	238	435	154	355	1351	281
Ornamental Herbaceous Plants	192	102	67	292	508	185	435	1655	345
Cotton (banding)	109	61	39	161	305	105	241	915	191
Beets, Asparagus, Eggplant	625	610	309	875	3050	680	1306	4965	1034
Strawberry,	417	203	137	648	1017	396	967	3678	766
Peanuts	93	61	37	147	305	99	211	804	167
Apple, Cherry, Citrus, Nectarine, Peaches	39	20	13	58	100	37	86	331	68
Grapes	49	31	19	74	155	50	109	414	86
Raspberry	417	203	137	583	1017	371	871	3310	689
Tobacco	35	20	13	53	100	35	81	301	64
Pineapple	64	31	21	96	155	59	147	552	116
Leather Leaf Fern	250	122	82	389	610	237	580	2207	460
Ornamental Woody Shrubs and Vines	227	122	79	350	610	222	522	1986	414
Turf, Golf Course and Sod Farm Turf	29	15	10	44	75	28	64	305	53
Banana [24(C)]	227	122	79	350	610	222	522	1986	414
Scenario (V): Soil Injection									
Cotton	No Data	No Data	No Data	No Data	No Data	No Data	No Data	No Data	No Data
Scenario (VI): Tractor-Drawn Granular Application									
Commercial and Industrial Turf, Golf Course Turf	35	6.8	5.7	93	35	25	156	61	44
Pineapple	96	20	17	258	100	72	442	169	122
Protea	357	76	63	945	380	271	1632	626	452
Leatherleaf Fern, Anthurium	357	68	57	921	340	248	1591	610	441
Ornamental Shade Trees, Ornamental Herbaceous Plants, Ornamental Woody Shrubs and Vines	179	31	26	461	155	116	795	305	220

Application Targets (commodities)	Baseline			PPE			Engineering Controls		
	Dermal MOE	Inhalation MOE	Total (Aggregate) MOE	Dermal MOE	Inhalation MOE	Total (Aggregate) MOE	Dermal MOE	Inhalation MOE	Total (Aggregate) MOE
Iris, Lily, Narcissus	357	68	57	921	340	248	1591	610	441
Cabbage, Pepper, Chinese Cabbage, Okra, Brussels Sprouts	500	102	84	1279	508	364	2210	847	612
Peanuts	119	23	20	307	115	84	530	203	147
Strawberries (Production and Nonbearing Nursery Stock), Eggplant	833	203	163	2303	1017	705	3977	1525	1102
Cabbage, Brussels Sprouts	500	102	84	1279	508	364	2210	847	612
Strawberries (Production and Nonbearing Nursery Stock)	625	122	102	1706	610	449	2946	1130	817
Garlic	417	76	64	1023	380	277	1768	678	490
Ornamental Herbaceous Plants	357	68	57	921	340	248	1591	610	441

Note: In the last column, all MOEs in bold are below 100 (this is considered a risk estimate that exceeds the Agency's level of concern)

Table 16. Pineapples Harvesters/Workers Postapplication Assessment (MRID # 419017-01)

DAT[1]	DFR (µg/cm2)[2]	Dermal Dose (mg/kg/day) [3]	Short- and Intermediate-Term MOE [4]
Exposure Activities [Tc = 2,500 cm^2/hr (Pineapple Harvesting)][5]			
0	1.16	0.33	8
5	0.52	0.15	17
7	0.38	0.11	23
10	0.23	0.067	37
14	0.12	0.035	71
16	0.09	0.026	96
17	0.08	0.022	110
21	0.04	0.011	230

[1]DAT is days after treatment based on an application rate of 10 lbs ai/acre for 90 days, then re-apply one more time at the same rate.

[2] DFR (µg/cm^2) = Ln DFR = 0.147 - 0.160 (DAT), calculated from the statistical software package JMP, utilizing the study data from all three sites. Dislodgeable foliar residues that are available from the application Rate [lb ai/Acre (from the study- MRID# 419017-01, the average amount of residues on the same day from three sites in Hawaii] that was applied to pineapple crops; which dissipated over time.

[3]Dermal Dose (mg/kg/day) = [DFR (µg/cm^2) x Tc (cm^2/hr) x (1 mg/1,000 µg unit conversion) x 8 hours/day] / Body Weight (BW kg). For adult, BW = 70kg.

[4]MOE = NOEL (mg/kg/day)/Dermal Dose (mg/kg/day); Short-term, and Intermediate-term NOEL = 2.5 mg/kg/day.

[5]The dermal transfer coefficient is assumed to be 2,500 cm^2/hr for harvesting pineapples for 8 hours /day of exposure.

Table 17. Golf Course Turf Surrogate Postapplication Range-Finder Assessment

DAT [1]	DFR (µg/cm2) [2]	Dermal Dose (mg/kg/day) [3]	Short-Term MOE [4]
Exposure Activities [Tc = 100 cm^2/hr (Low activity for Golfers)] [e]			
0	5.6 (5%)	0.032	78 (Adult)
0	5.6 (5%)	0.051	49 (Adolescent-12+)

[1]DAT is days after treatment based on an application rate of 2.3 $X10^{-4}$ lb ai/ ft^2 (10 lbs ai/acre).

[2]DFR (µg/cm^2) = Rate (lb ai/ft^2) x (weight conversion factor to convert the lbs a.i. in the application rate to µg for the DFR value = 4.54x 10^8 µg/lb) x (area unit conversion factor = 1.08 x 10^{-3} ft^2/cm^2) x percent (5 percent assumed) of rate available as dislodgeable.

[3]Dermal Dose (mg/kg/day) = [TTR (µg/cm^2) x Tc (cm^2/hr) x (1 mg/1,000 µg unit conversion) x 4 hours/day] / Body Weight (BW kg). For adult, BW = 70kg; and for the adolescent (12 +), BW = 44kg

[4]MOE = NOEL (mg/kg/day)/Dermal Dose (mg/kg/day); Short-term NOEL = 2.5 mg/kg/day.

[5]The dermal transfer coefficient is assumed to be 1,00 cm^2/hr for golfers for 4 hours / 18 holes of golf of exposure.

Attachment 1. Toxicology Chapter

Memorandum

Subject: EPA Id No.: 100601. Fenamiphos. Toxicology Branch Chapter for the RED.

PC Code: 100601
DP Barcode: D254614
ReRegistration Case 0333

From: John Doherty
ReRegistration Branch III
Health Effects Division 7509C

Through: Jess Rowland
Branch Chief
ReRegistration Branch III
Health Effects Division 7509C

To: Todd Peterson
ReRegistration Branch 2
Special Review and ReRegistration Division 7507C

and

Julianna Cruz
ReRegistration Branch III
Health Effects Division 7509C

Attached is the Toxicology Section for the RED chapter for fenamiphos. An electronic copy is available on the LAN.

Part I. **Hazard Assessment.**

The toxicological data base on fenamiphos is adequate and will support ReRegistration eligibility. Note that in accordance with current HED Policy (M. Stasikowski, 9/24/98), the terms No Observable Effect Level (NOEL) and Lowest Observable Effect Level (LOEL) have been replaced with No Observable Adverse Effect Level (NOAEL) and Lowest Observable Adverse Effect Level (LOAEL).

a. Acute Toxicity of Fenamiphos[1]

Table 1: Acute Toxicity, Technical Fenamiphos

Test	Result	Category
Acute Oral LD_{50} (rat)	2.7 mg/kg M[2] 3.0 mg/kg F[3]	I
Acute Dermal LD_{50} (rabbit)	225 mg/kg M 178.8 mg/kg F	I
Acute Inhalation LC_{50} (rat)	> 0.1 mg/L (nominal but 0.02 μL analytical)	II
Eye Irritation (rabbit)	mild irritation	III
Dermal Irritation (rabbit)	not irritating	IV
Skin Sensitization (guinea pig)	negative	-

[1] Based on the technical grade fenamiphos. [2] M = Male; [3] F = Female

The LD_{50} for 88% fenamiphos from an acute oral Sprague-Dawley rat study was 2.7 mg/kg and 3.0 mg/kg in males and females, respectively (Guideline 81-1; MRID # 00033831). Similar oral LD_{50} values were obtained with fenamiphos in mice, rabbits, cats, dogs, and hens. In contrast, oral LD_{50} values for most metabolites of fenamiphos exceeded 1000 mg/kg. (HED Doc. # 1310).

The LD_{50} for technical fenamiphos from an acute dermal study was 225 mg/kg in male and 178.8 mg/kg in female New Zealand white rabbits, respectively (Guideline 81-2; MRID # 00037962). The LC_{50} for a rat inhalation study with 89.9% fenamiphos in THO/W74 rats of both sexes was > 0.1 mg/L (based on the nominal concentration but 0.02 μg/L based on the analytical concentration) for a 4-hour exposure (Guideline 81-3; MRID # 00154492). Ocular application of fenamiphos to rabbits produced mild chemosis and iritis with category III toxicity (Guideline 81-4; MRID # 00082111). A primary dermal irritation study indicated that fenamiphos was not a skin irritant (Guideline 81-5; MRID # 00082111). No dermal sensitization occurred with 90.2% fenamiphos in Hartley guinea pigs (Guideline 81-6; MRID # 00148464). Fenamiphos was not neurotoxic when administered in a single oral dose to white leghorn hens in an acute delayed neurotoxicity study (Guideline 81-7; MRID # 00057606).

b. Subchronic Toxicity

Subchronic studies were conducted in two strains of rats following dietary exposures. In one study Wistar rats received diets containing fenamiphos at doses of 0, 4, 8, 16, or 32 ppm (equivalent to 0, 0.2, 0.4, 0.8 or 1.6 mg/kg/day, respectively) for 13 weeks. The NOAEL was 0.2 mg/kg/day based on plasma and red cell cholinesterase inhibition at 0.4 mg/kg/day (LOAEL). (Guideline 82-1; MRID # 00117403). In the other study, Fisher 344 rats were fed fenamiphos in the diet at doses of 0, 0.36, 0.6, or 1.0 ppm (0, 0.018, 0.03, or 0.05 mg/kg/day, respectively) for 13 weeks. The NOAEL was 0.05 mg/kg/day, highest dose tested) [Guideline 82-1; MRID # 00133475 (HED Doc. #3606)].

Two subchronic studies were available following dietary exposures to beagle dogs. In one study, dogs received fenamiphos in the diet at doses of 0, 1, 2, or 5 ppm (0, .025, 0.05, or 0.125 mg/kg/day, respectively) for 90-days. The NOAEL was 0.025 mg/kg/day and the LOAEL was 0.05 mg/kg/day, based on dose-related plasma cholinesterase inhibition. Erythrocyte cholinesterase inhibition and growth depression occurred at the highest dose tested (0.125 mg/kg/day) (Guideline 82-1; MRID # 00119238, 0119957 [HED Doc. # 1310]). In a second study, the doses tested were 0, 0.6, 1.0, or 1.7 ppm (0, 0.015, 0.025, 0.042 mg/kg/day, respectively) for 90-days. The NOAEL was 0.025 mg/kg and the LOAEL was 0.042 mg/kg/day based on depressed plasma cholinesterase activity (Guideline 82-1; MRID # 0154493 [HED Doc. # 4602]).

In a 21-day dermal toxicity study, groups of New Zealand white rabbits (2/sex/dose) received repeated dermal applications of technical fenamiphos in an aqueous formulation (89.8%) at doses of 0, 0.5, 2.5, and 10 mg/kg/day, 6 hours/day, 5 days/week for three weeks. Blood cholinesterase was determined on days 0, 10, and 15 of the study. At 10 mg/kg, plasma cholinesterase was decreased in male and female rabbits on day 10 by 42% and 40%, respectively; blood cholinesterase was decreased in male and female rabbits on day 10 by 23% and 41%, respectively; brain cholinesterase was decreased in male and female rabbits on day 10 by 11% and 23%, respectively (non-abraded skin for all effects). At 2.5 mg/kg/day, plasma cholinesterase in female rabbits was decreased by 30% on day 10; brain cholinesterase was decreased in female rabbits on day 15 by 11%. No decreases in cholinesterase were noted in male rabbits at 2.5 mg/kg/day (non-abraded skin for all effects). The NOAEL was determined to be 2.5 mg/kg/day based on the marginal effects observed at this dose. Inhibition of plasma and brain cholinesterase in female rabbits at 10 mg/kg/day on day 10. At the 10 mg/kg/day dose level on day 10, inhibition of plasma, blood, and brain cholinesterase was observed in both male and female rabbits, whereas at the 2.5 mg/kg/day dose on day 10, only inhibition of plasma cholinesterase (30% decrease) in females was observed. At the 2.5 mg/kg/day dose, the effect on brain cholinesterase (11% decrease) in females could have been the result of unusually high control values. In addition, variability in the response of plasma and red cell cholinesterase was observed at 2.5 mg/kg/day. Therefore, the 2.5 mg/kg/day dose was considered a NOAEL and appropriate for risk assessments (MRID # 00154497; HED Doc. # 4531, 5722).

In a 21-day inhalation study, Wistar rats (10/sex/concentration) were exposed "nose only" to concentrations of fenamiphos at 0, 0.03, 0.25 or 3.5 μg/L for 6-hours/day, 5 days/week over a 3-week period. Ninety eight percent of the particles were 3 or less. The NOAEL was 0.25 μg/L

and the LOAEL was 3.5 μg/L based on inhibition of plasma cholinesterase activity in males (42-47%) and females (72-78%) and erythrocyte activity in females (15-19%) (Guideline 82-4; MRID #40774809 [HED Doc. # 11035]).

c. Chronic Toxicity

In a chronic toxicity study, beagle dogs (4/sex/dose) were fed diets containing fenamiphos (technical) at 0, 1.0, 3.0 or 12.0 ppm (0, 0.03, 0.08 or 0.3 mg/kg/day respectively) for 12 months. Based on plasma cholinesterase inhibition of 25-32% in males and 20-26% in females, the LOAEL was 0.03 mg/kg/day, the lowest dose tested; a NOAEL was not established for this effects. For systemic toxicity, the NOAEL was 0.08 mg/kg/day and the LOAEL was 0.3 mg/kg/day based on anemia observed in males (MRID # 42183601).

In a follow-up study, to establish a NOAEL for plasma cholinesterase activity, beagle dogs (4/sex/dose) received fenamiphos (technical) in the diet at 0.5 ppm (0.0108 and 0.0115 mg/kg/day, in males and females, respectively) for 180 days. No statistically significant inhibition of plasma or erythrocyte activity was seen at this dose (MRID # 42684801)

The combination of these two studies yielded a NOAEL of 0.01 mg/kg/day and a LOAEL of 0.03 mg/kg/day for inhibition cholinesterase activity (Guideline 83-1(a); MRID # 42183601; 42684801 [HED Doc. # 10241]).

In a combined chronic toxicity/carcinogenicity study Fischer 344 rats (60/sex/dose) were fed diets containing fenamiphos at 0, 2, 10, or 50 ppm (equivalent to 0, 0.098, 0.46 or 2.45 mg/kg/day for males and 0, 0.12, 0.6, or 3.36 mg/kg/day for females, respectively) for 104 weeks. Inhibition of plasma and red cell cholinesterase activity was seen at all dose levels including the lowest dose (2 ppm); a NOAEL was not established for this effect. For systemic toxicity the NOAEL was 10 ppm (0.46 mg/kg/day in males and 0.6 mg/kg/day in females)(and the LOAEL was 50 ppm (2.45 mg/kg/day in males and 3.36 mg/kg/day in females) based upon reduction in body weight gain and food consumption, as well as decreased liver and increased lung weights. This was accompanied by granulomatous inflammation of the lungs in both sexes at the high dose level. There was no evidence of carcinogenicity in either sex of rats. (Guidelines 83-1, 83-2; 83-5 MRID # 00161361, 40329601 [HED Doc. # 3331, 3606, 5682, 5722]).

d. Carcinogenicity

The carcinogenic potential of fenamiphos has been evaluated following long term exposures to mice and two strains of rats.

In a carcinogenicity study, CD albino mice (50/sex/dose) received diets containing fenamiphos at doses of 0, 2, 10, or 50 ppm (0, 0.2, 1.0, or 5.0 mg/kg/day, respectively). Body weight was reduced at the highest dose level. There was no evidence of carcinogenicity in either sex (Guidelines 83-1(b), 83-2(b); MRID # 00098614 [HED Doc. # 2241, 5722]).

In Fischer rats, (as discussed above in B.1.c. chronic toxicity), no evidence of carcinogenicity was seen in males or females following dietary exposures at 0, 2, 10, or 50 ppm

for 104 weeks (Guidelines 83-1, 83-2; MRID # 00161361, 40329601 [HED Doc. # 3331, 3606, 5682, 5722])..

In Wistar rats, dietary administration of fenamiphos at 0, 3, 10, or 30 ppm (0.15, 0.5, or 1.5 mg/kg/day) produced no evidence of carcinogenicity in either sex (Guideline 83-2(a); MRID # 00038490 [HED Doc. # 1314]).

On May 20, 1993, the HED RfD Peer Review Committee determined that the high dose levels tested in rats and mice were adequate to assess the carcinogenic potential of fenamiphos.

e. Developmental Toxicity

In a developmental toxicity study with CD rats, pregnant animals were given oral doses of Fenamiphos at 0, 0.25, 0.85 or 3.0 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOAEL was 0.85 mg/kg/day and the LOAEL was 3.0 mg/kg/day based on increased mortality, reduction in body weight gain and food consumption, cholinergic signs and plasma and erythrocyte cholinesterase activity. For developmental toxicity, the NOAEL was 3.0 mg/kg/day (HDT); a LOAEL was not established (Guideline 83-3(a); MRID # 41225401 [HED Doc. # 7669]).

In a developmental toxicity study, artificially pregnant Chinchilla rabbits received oral doses of fenamiphos at 0, 0.1, 0.5 or 2.5 mg/kg/day during gestation days 6 through 18. For maternal toxicity the NOAEL was 0.5 mg/kg/day and the LOAEL was 2.5 mg/kg/day based on cholinergic signs. For developmental toxicity, the NOAEL was 2.5 mg/kg/day (HDT); a LOAEL was not established. The HED RfD Committee considered the skeletal anomalies at 2.5 mg/kg/day to be an isolated incident and not treatment-related (Guideline 83-3(b); MRID # 40347602 [HED Doc. # 6666]).

f. Reproductive Toxicity

In a 2-generation reproduction study, when administered in the diet at 0, 2.5, 10 or 30 ppm (0, 0.17, 0.64 or 2.8 mg/kg/day for males and 0, 0.2, 0.73 or 3.2 mg/kg/day for females) to Sprague-Dawley rats, no increased sensitivity to pups over the adults was seen. For parental systemic toxicity, the NOAEL was 0.17 mg/kg/day for males and <0.2 mg/kg/day for females. The LOAEL was 0.64 mg/kg/day for males and 0.2 mg/kg/day for females. In both sexes, the LOAELs were based on inhibition of plasma and RBC cholinesterase activity. For systemic (non-cholinergic) toxicity to the offspring and for reproductive toxicity, the NOAELs were 3.2 mg/kg/day (HDT); LOAELs were not established. Guideline 83-4; MRID # 41908901, 42491701 [HED Doc. # 9473]).

In a 3-generation reproduction study, when administered in the diet at 0, 3, 10 or 30 ppm (0, 0.15, 0.5 or 1.5 mg/kg/day, respectively) to rats, no increased sensitivity to pups over the adults was seen. For parental toxicity, the NOAEL was 0.5 mg/kg/day and the LOAEL was 1.5 mg/kg/day based on reduced body weight gain in F2b males. For reproductive and offspring toxicity, the NOAEL was 1.5 mg/kg/day (HDT); a LOAEL was not established. (Guideline 83-4; MRID # 41908901, 42491701 [HED Doc. # 9473]).

g. Neurotoxicity

In an acute neurotoxicity screening battery in rats, fasted (overnight) male and female Wistar rats (18/sex/dose) were given a single oral (gavage) dose of fenamiphos at 0, 0.4, 1.6, or 2.4 mg/kg (analytically confirmed doses: 0, 0.37, 1.52, and 2.31 mg/kg). The main study animals (12 rats/sex/dose, except the high-dose male group which contained 15 rats) were used for a routine neurotoxicity screening battery with behavioral testing at the peak time of effect (25 min postdosing) and at days 7 and 14 postdosing; neuropathological examination was carried out at terminal sacrifice (day 14). Plasma, RBC and brain cholinesterase activities were measured in 6 rats/sex/dose) at approximately 50 min postdosing. No treatment-related changes were noted in mean body weights, absolute and relative brain weights and the incidences of gross and neurohistopathological lesions. At the high-dose, fenamiphos toxicity was observed within 21 to 31 min postdosing (lethality 7/15 males, 1/12 females), with clinical signs of cholinesterase inhibition persisting to approximately 2 hr 45 min postdosing. At 4 to 8 hr postdosing, all treatment-related clinical signs were absent. Although plasma and RBC ChE activities were markedly and rapidly (50 min postdosing) inhibited, brain ChE was unaffected. The following treatment-related effects were observed: at 2.31 mg/kg lethality in males and females, muscle fasciculations, gait incoordination, nasal and oral staining, constricted pupils, salivation, lacrimation (females only), and piloerection, statistically significant decreases in plasma and RBC ChE activities, and decreased motor and locomotor activities in males; at 1.52 mg/kg muscle fasciculations in males, statistically significant decreases in plasma and RBC ChE activities and at 0.37 mg/kg statistically significant decreases in plasma ChE in females and RBC ChE in males with a non-significant decrease in plasma ChE in males. Based on the results of this study (inhibition of plasma and RBC), the LOAEL was established at 0.37 mg/kg; the NOAEL was not established (Guideline 81-8; MRID 44041501).

In a subchronic neurotoxicity screening battery male and female Wistar rats (12/sex/dose) were fed diets containing fenamiphos at 0 (basal diet), 1, 10, or 50 ppm (equivalent to 0, 0.06, 0.61, or 3.13 mg/kg/day, males; 0, 0.08, 0.8, 3.98 mg/kg/day, females) for at least 13 weeks. Routine neurotoxicity screening battery consisting of Functional Observational Battery and motor activity measurements were performed at prestudy and after 4, 8 and 13 weeks of treatment. Gross pathology (all animals) and neuropathological (6/sex/dose) examinations were carried out at terminal sacrifice. Plasma and RBC cholinesterase activities were measured in 6/sex/dose at Week 4; plasma, RBC and brain cholinesterase activities were measured on animals not selected for neuropathological examination at Week 15. No treatment-related changes were noted in mean body weights or absolute and relative brain weights. The incidences of gross and neuropathological finding of treated animals were comparable to controls. Dose-related increases in motor and locomotor activity were observed in females at Week 13. This effect was judged to be equivocal since a similar "dose-related" increase was observed during the pre-study evaluations. Additionally, none of the motor or locomotor activities achieved statistical significance. No treatment-related effects were observed in animals dosed at 1 ppm. At 10 ppm, decreases in plasma ChE activity at Week 4 and Week 15 and RBC ChE activity at Week 4 and Week 15. At 50 ppm, an increased incidence of muscle fasciculations in all females during weeks 1 to 3. Statistically significant decreases in plasma ChE activity at Week 4 and Week 15 and RBC ChE activity at Week 4 and Week 15. Brain ChE was slightly (but statistically significant) decreased (-12%) at Week 15 in females. Based on the results (inhibition of plasma and RBC

ChE) of this study, the LOAEL was established at 10 ppm (0.61 mg/kg/day, males; 0.8 mg/kg/day, females); the NOAEL was established at 1 ppm (0.06 mg/kg/day, males; 0.08 mg/kg/day, females) (Guideline 82-5; MRID 44041502 and 44051401[HED Document No.: 012019]).

h. Mutagenicity

Fenamiphos was not mutagenic in studies designed to detect gene mutations. These were the CHO/HGPRT assay in vitro (Guideline 84-2(a); MRID # 00159127) and the Ames reversion assay with S. typhimurium (Guideline 84-2(a); MRID # 40319001). Structural chromosomal aberrations were not found in the dominant lethal test in mice (Guideline 84-2(b); MRID # 00086981). The B. subtilis rec assay (MRID No.: 00161367[HED Document No.: 5682]) and the unscheduled DNA synthesis assay in primary rat hepatocytes were negative (Guideline 84-4; HED Doc. # 5682 and MRID # 40649101).

I. Metabolism

Metabolism studies in the rat indicated no major differences between oral and intravenously administered fenamiphos (Guideline 85-1; MRID #'s 41194901 and 41194902). Orally administered compound was rapidly absorbed, and compounds given by both routes were immediately metabolized and excreted. The major metabolites were sulfoxides and sulfates, nine of which were found in urine, with only a single major metabolite in feces. Within 48 hours after oral or i.v. dosing with radiolabelled compound, 93 to 100% of the administered dose was found in urine, 1.5 to 3.8% in feces, and less than 0.1% in CO_2. Tissue levels of radioactivity were highest at 48 hours in liver, kidneys and skin. Based on the data, a metabolic pathway was proposed for fenamiphos.

Attachment 2. Toxicology Endpoint Selection Document

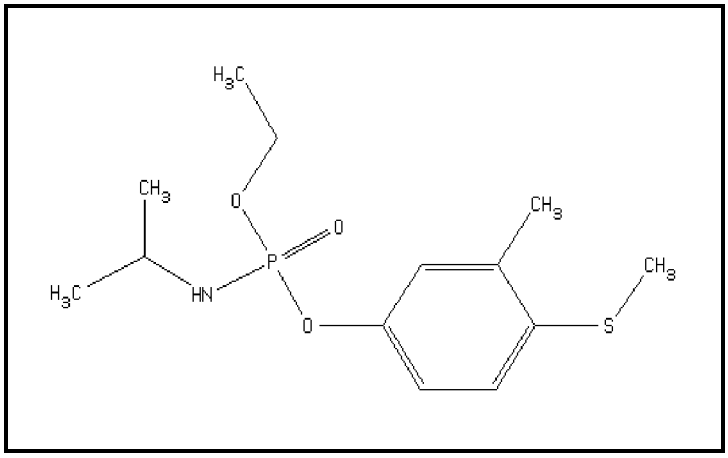
HED DOC. NO. 013199
Document dated 08/08/96

TOXICOLOGY ENDPOINT SELECTION DOCUMENT -

REVISED

Chemical Name: **Fenamiphos**

PC Code: **100601**



The Health Effects Division Less Than Life-Time Peer Review Committee considered the available toxicology data for this chemical at a meeting held on November 28, 1995. Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

TOXICOLOGIST: _____Date:_____

ACTING SECTION HEAD: _____Date:_____

ACTING BRANCH CHIEF: _____Date:_____

DERMAL ABSORPTION DATA
No studies were available to assess dermal absorption. Assume 100% absorption.

****

ACUTE DIETARY ENDPOINT (ONE DAY)

Study Selected - Acute Neurotoxicity in Rats Guideline No.: OPPTS 870.6200; OPP §81-8

MRID No.: 44041501

Summary: Fasted (overnight) male and female Wistar rats (18/sex/dose) were orally gavaged once with Fenamiphos at 0, 0.4, 1.6, or 2.4 mg/kg (actual doses of 0, 0.37, 1.52, and 2.31 mg/kg). No treatment related changes were noted in mean body weights, absolute and relative brain weights and the incidences of gross and neurohistopathological lesions. At all dose levels, toxicity from fenamiphos was observed within 21 to 31 minutes post-dosing and persisted to approximately 2 hours 45 minutes post-dose. At 2.31 mg/kg, lethality was observed in 7/15 males and 1/12 females. Muscle fasciculations, gait incoordination, nasal and oral staining, constricted pupils, salivation, lacrimation (females only) and piloerection were also observed. Also at this dose, a statistically significant decrease in plasma (61% in males, 85% in females) and RBC cholinesterase (76% in males, 80% in females) was observed, as was decreased motor (32%) and locomotor (41%) activities in males. At 1.52 mg/kg, muscle fasciculations in males were observed as were significant decreases in plasma (64% in males, 77% in females) and RBC cholinesterase (70% in males, 51% in females). At 0.37 mg/kg, significant decreases in plasma cholinesterase in females (55%) and and RBC cholinesterease in males (24%) were observed, as was a statistically nonsignificant decrease in plasma cholinesterase in males (23%). Based on the results of this study (inhibition of plasma and RBC cholinesterase), the LOEL was established at 0.37 mg/kg; a NOEL was not established.

Dose and Endpoint: A dose of 0.12 mg/kg, obtained by using the LOEL of 0.37 mg/kg, and an additional safety factor of 3 because of the use of a LOEL. The LOEL is based on the statistically significant decrease in red cell cholinesterase in male rats (24%), the statistically nonsignificant decrease in plasma cholinesterase in male rats (23%), and the significantly decreased plasma cholinesterase in female rats (55%).

Comments about study and/or endpoint: Because a NOEL was not achieved in this study, risk assessment is done by using the LOEL and an additional Modifying Factor of 3.

This risk assessment is required.

****

SHORT TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 TO 7 DAYS)

Study Selected - Guideline No.: 21-Day Dermal Toxicity (§82-2)

MRID No.: 00154497

Summary: Technical fenamiphos in an aqueous formulation (89.8%) was applied to the clipped back area of New Zealand white rabbits (2/sex/dose) at doses of 0, 0.5, 2.5, and 10 mg/kg body weight. Exposures were for 6 hours/day, 5 days/week, for 3 weeks. Blood cholinesterase was determined on days 0, 10, and 15 of the study. At 10 mg/kg, plasma cholinesterase was decreased in male and female rabbits on day 10 by 42% and 40%, respectively; blood cholinesterase was decreased in male and female rabbits on day 10 by 23% and 41%, respectively; brain cholinesterase was decreased in male and female rabbits on day 10 by 11% and 23%, respectively (non-abraded skin for all effects). At 2.5 mg/kg/day, plasma cholinesterase in female rabbits was decreased by 30% on day 10; brain cholinesterase was decreased in female rabbits on day 15 by 11%. No decreases in cholinesterase were noted in male rabbits at 2.5 mg/kg/day (non-abraded skin for all effects).

Dose and Endpoint: NOEL/LOEL of 2.5 mg/kg/day, based on inhibition of plasma and brain cholinesterase in female rabbits at 10 mg/kg/day on day 10.

Comments about study and/or endpoint: At the 10 mg/kg/day dose level on day 10, inhibition of plasma, blood, and brain cholinesterase was observed in both male and female rats, whereas at the 2.5 mg/kg/day dose on day 10, only inhibition of plasma cholinesterase (30% decrease) in females was observed. At the 2.5 mg/kg/day dose, the effect on brain cholinesterase (11% decrease) in females could have been the result of unusually high control values. In addition, variability in the response of plasma and red cell cholinesterase was observed at 2.5 mg/kg/day. Therefore, the 2.5 mg/kg/day dose was considered a NOEL/LOEL as the effects at this dose were considered marginal. **An MOE of 100 is adequate** for this risk assessment.

This risk assessment is required.

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INTERMEDIATE TERM OCCUPATIONAL OR RESIDENTIAL (1 WEEK TO SEVERAL MONTHS)

Study Selected - Guideline No.: Same as the short-term dermal

MRID No.: 00154497

Summary: See Short-term

Endpoint and dose for use in risk assessment: NOEL/LOEL of 2.5 mg/kg/day, based on inhibition of plasma and brain cholinesterase in female rabbits at 10 mg/kg/day on day 10.

Comments about study and/or endpoint: At the 10 mg/kg/day dose level on day 10, inhibition of plasma, blood, and brain cholinesterase was observed in both male and female rats, whereas at the 2.5 mg/kg/day dose on day 10, only inhibition of plasma cholinesterase (30% decrease) in females was observed. At the 2.5 mg/kg/day dose, the effect on brain cholinesterase (11% decrease) in females could have been the result of unusually high control values. In addition, variability in the response of plasma and red cell cholinesterase was observed at 2.5 mg/kg/day. Therefore, the 2.5 mg/kg/day dose was considered a NOEL/LOEL as the effects at this dose were considered marginal. **An MOE of 100 is adequate** for this risk assessment.

This risk assessment is required.

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CHRONIC OCCUPATIONAL OR RESIDENTIAL (SEVERAL MONTHS TO LIFETIME)

Study Selected - Guideline No.: Chronic Toxicity in Dogs (§83-1)

MRID No.: 42183601, 42684801.

Summary: In a chronic toxicity study, beagle dogs (4/sex/dose) were fed diets containing fenamiphos (Technical, 89.5%) at 0, 1.0, 3.0 or 12.0 ppm for 12 months (MRID # 42183601). Based on plasma cholinesterase depression of 25-32% in males and 20-26% in females, the LOEL was 1 ppm (0.03 mg/kg/day), the LDT; a NOEL was not established for plasma ChEI. The systemic NOEL was 3 ppm (0.089 mg/kg/day in males and 0.083 mg/kg/day in females) and the LOEL was 12 ppm (0.308 and 0.349 mg/kg/day for males and females, respectively).

In a follow-up study (MRID No. 42684801), to establish a NOEL for plasma ChEI, 4 male and 4 female beagle dogs were fed diets containing fenamiphos (Technical, 88.4%) at 0.5 ppm (0.0108 and 0.0115 mg/kg/day, in males and females, respectively) for 180 days. Plasma and erythrocyte ChE determinations were made three times at one week interval prior to treatment, at one month intervals during treatment and at termination of the study. No statistically significant inhibition of plasma or erythrocyte ChE activity was seen at this dose. The NOEL for plasma ChEI was 0.5 ppm (0.0108 mg/kg/day).

Dose and Endpoint for use in risk assessment: NOEL of 0.01 mg/kg/day for plasma cholinesterase inhibition observed at 0.03 mg/kg/day.

Comments about study and/or endpoint: This study/endpoint/dose was also used to establish the RfD.

This risk assessment is required.

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INHALATION EXPOSURE (ANY TIME PERIOD):

Study Selected - Guideline No.: 21-Day Inhalation (§82-4)

MRID No.: 40774809

Summary: Technical fenamiphos (92.2%) was administered nose-only to groups of ten Wistar rats/sex/dose at doses of 0, 0.03, 0.25, and 3.5 μg/L for 6 hours/day, 5 days/week, for 3 weeks. The NOEL was 0.25 μg/L, and the LEL was 3.5 μg/L based on decreased plasma cholinesterase in males (42-47%) and females (72-78%).

Dose and Endpoint for use in risk assessment: NOEL of 0.25 μg/L, based on inhibition of plasma cholinesterase observed at 5 days at the 3.5 μg/L dose.

Comments about study and/or endpoint: None

This risk assessment is required.

CANCER CLASSIFICATION AND BASIS: "Group E" carcinogen (no evidence of carcinogenicity) based on acceptable studies conducted in two animal species.

Q_1* = N/A

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R_FD AND BASIS: On the basis of a NOEL of 0.01 mg/kg/day for plasma cholinesterase inhibition observed at 0.03 mg/kg/day in a 1-year feeding study in dogs, an RfD of 0.0001 mg/kg/day was calculated, using an uncertainty factor of 100.

NOEL for critical study:0.01 mg/kg/day

Study Type - Guideline No.: Chronic Toxicity in Dogs (§83-1)

MRID No.: 421836-01, 426848-01.

Acute Toxicity of Fenamiphos (Technical)

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	00033831	LD_{50} = 2.7 mg/kg (M) 3.0 mg/kg (F)	I
81-2	Acute Dermal	00037962	LD_{50} = 225 mg/kg (M) 178.8 mg/kg (F)	I
81-3	Acute Inhalation	00154492	LC_{50} = 0.1 mg/l	II
81-4	Primary Eye Irritation	111667	Mild irritant	III
81-5	Primary Skin Irritation	111667	Non-irritant	IV
81-6	Dermal Sensitization	00148464	Non-sensitzer	NA

Attachment 3. Fenamiphos: FQPA Requirement - Report of the Hazard Identification Assessment Review Committee

DATE: September 18, 1997

MEMORANDUM

SUBJECT: **FENAMIPHOS - *FQPA REQUIREMENT* -** Report of the Hazard Identification Assessment Review Committee.

FROM: Jess Rowland
Branch Senior Scientist,
Science Analysis Branch, Health Effects Division (7509C)

THROUGH: K. Clark Swentzel
Chairman, Hazard Identification Assessment Review Committee
Toxicology Branch II, Health Effects Division (7509C)

TO: Karen Whitby
Chief, Risk Characterization & Analysis Branch, Health Effects Division (7509C)

PC Code: 100601

BACKGROUND: On September 2, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Fenamiphos with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Fenamiphos as required by the Food Quality Protecting Act (FQPA) of 1996. The FQPA requirement was not addressed in the Reregistration Eligibility Document. The Committee's decisions are summarized below.

CC: Rick Whiting, Science Analysis Branch
Caswell File
LAN storage

A. INTRODUCTION

The Health Effects Division's Hazard Identification Assessment Review Committee met to evaluate the toxicology data base of Fenamiphos with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Fenamiphos as required by the Food Quality Protecting Act (FQPA) of 1996. The FQPA requirement was not addressed in the Reregistration Eligibility Document.

B. RESULTS: Evaluation of the toxicology data base indicated the following:

1. Neurotoxicity

In an acute delayed neurotoxicity study, no clinical signs of neurotoxicity or neuropathology were seen in hens following single oral doses of Fenamiphos at doses up to and including 10 mg/kg. The Committee noted that this study did not assess the potential of Fenamiphos to inhibit neurotoxic esterase (NTE) in hens (HED Doc. No. 001308).

No treatment-related pathological lesions were seen in the central or peripheral nervous systems in an acute neurotoxicity study in Wistar rats following single oral doses at 0, 0.4, 1.6 or 2.4 mg/kg/day or in the subchronic neurotoxicity study in Fisher 344 rats following dietary administration at dose levels of 0.08, 0.8 or 3.98 mg/kg/day for 90-days. In the acute study, the LOEL was 0.4 mg/kg/day based on plasma and red blood cell (RBC) ChE inhibition (ChEI); a NOEL was not established. In the subchronic study, the NOEL was 0.08 mg/kg/day and the LOEL was 3.98 mg/kg/day based on plasma and RBC ChEI (MRID Nos. 44041501 and 44051401).

2. Developmental Toxicity

The developmental toxicity studies in rats and rabbits showed no evidence of additional sensitivity to young rats or rabbits following pre-or postnatal exposure to Fenamiphos and comparable NOELs were established for adults and offspring.

In a developmental toxicity study with CD rats, pregnant animals were given oral doses of Fenamiphos at 0, 0.25, 0.85 or 3.0 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 0.85 mg/kg/day and the LOEL was 3.0 mg/kg/day based on increased mortality, reduction in body weight gain and food consumption, cholinergic signs and plasma and RBC ChEI. For developmental toxicity, the NOEL was 3.0 mg/kg/day (HDT); a LOEL was not established (MRID No. 41225401).

In a developmental toxicity study, artificially pregnant Chinchilla rabbits received oral doses of Fenamiphos at 0, 0.1, 0.5 or 2.5 mg/kg/day during gestation days 6

through 18. For maternal toxicity the NOEL was 0.5 mg/kg/day and the LOEL was 2.5 mg/kg/day based on cholinergic signs. For developmental toxicity, the NOEL was 2.5 mg/kg/day (HDT); a LOEL was not established (MRID No. 40347602).

3. Reproductive Toxicity

In a 2-generation reproduction study, when administered in the diet at 0, 2.5, 10 or 30 ppm (0, 0.17, 0.64 or 2.8 mg/kg/day for males and 0, 0.2, 0.73 or 3.2 mg/kg/day for females) to Sprague-Dawley rats, no increased sensitivity to pups over the adults was seen. For parental systemic toxicity, the NOEL was 0.17 mg/kg/day for males and <0.2 mg/kg/day for females. The LOEL was 0.64 mg/kg/day for males and 0.2 mg/kg/day for females. In both sexes, the LOELs were based on inhibition of plasma and RBC cholinesterase activity. For toxicity to the offspring and for reproductive toxicity, the NOELs were 3.2 mg/kg/day (HDT); LOELs were not established (MRID Nos.41908901 and 42491701).

In a 3-generation reproduction study, when administered in the diet at 0, 3, 10 or 30 ppm (0, 0.15, 0.5 or 1.5 mg/kg/day, respectively) to rats, no increased sensitivity to pups over the adults was seen. For parental toxicity, the NOEL was 0.5 mg/kg/day and the LOEL was 1.5 mg/kg/day based on reduced body weight gain in F1 males. For reproductive and offspring toxicity, the NOEL was 1.5 mg/kg/day (HDT); a LOEL was not established (MRID No.00037979).

4. Developmental Neurotoxicity

There are sufficient data available to adequately assess the potential for toxicity to young animals following pre-and/or post-natal exposure to Fenamiphos. These include acceptable developmental toxicity studies in rats and rabbits as well as 2-generation and 3-generation reproduction studies in rats. In addition, no treatment-related neuropathology was seen in studies conducted in hens or rats (acute and subchronic). Therefore, based upon a weight-of-the-evidence consideration of the data base, the Committee determined that a developmental toxicity study in rats is not required

5. Reference Dose

A Reference Dose (RfD) of 0.0001 mg/kg/day was derived from the NOEL of 0.01 mg/kg/day and an Uncertainty Factor (UF) of 100. The NOEL was based on plasma ChEI observed at 0.3 mg/kg/day in a 1-year feeding study in dogs. The UF of 100 included a 10 to account for intra-species and a 10 for inter-species variations.

6. Data Gaps

None

C. CONCLUSIONS

The Committee's conclusions on the Uncertainty Factors for acute and chronic dietary risk assessments are as follows:

1. Acute Dietary Risk Assessment

The endpoint selected for acute dietary risk assessment is based on inhibition of plasma (males and females) and red blood cell (males) cholinesterase activity at 0.37 mg/kg/day (LOEL) in an acute neurotoxicity study with rats. A NOEL was not established in this study. Since the dose identified is a LOEL, an additional UF of 3 was recommended.

Therefore, for acute dietary risk assessment, the Committee determined that the **10 x** factor to account for enhanced sensitivity to infants and children (as required by FQPA) **should be reduced by 3-fold for a total UF of 300** (10 for inter-species variability x 10 for intra-species variability x 3 for lack of a NOEL). Consequently, **A MOE of 300 is required** to ensure protection of this population from exposure to Fenamiphos for the following reasons:

(I) The endpoint identified was cholinesterase inhibition in adult rats.

(ii) There was no evidence of maternal or developmental toxicity attributable to a an acute (single dose) *in utero* exposure of Fenamiphos in developmental toxicity studies.

(iii) An additional UF of 3 was applied to account for the lack of a NOEL in the critical study.

2. Chronic Dietary Risk Assessment

The endpoint selected for chronic dietary risk assessment is based on plasma ChEI observed at 0.3 mg/kg/day (LOEL) in a 1-year feeding study in dogs. The NOEL was 0.01 mg/kg/day. An UF of 100 was applied to the NOEL; 10 to account for intra-species and a 10 for inter-species variations. Thus a RfD of 0.0001 mg/kg/day was derived.

For chronic dietary risk assessments, the Committee determined that the **10 x** factor to account for enhanced sensitivity of infants and children (as required by FQPA) **should be removed.** The present **UF of 100 is adequate** to ensure the protection of this population from exposure to Fenamiphos. **Thus the RfD remains at 0.0001 mg/kg/day.** An UF of 100 is adequate since there was no indication of increased sensitivity to young animals following pre-and/or post-natal exposure to Fenamiphos as shown below:.

(I) Developmental toxicity studies showed no increased sensitivity to fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.
(ii) A 2-generation and a 3-generation reproduction toxicity studies in rats showed no increased sensitivity to pups as compared to adults.

Attachment 4. Hazard Assessment of the Organophosphates: Report of the Hazard Identification Assessment Review Committee

HAZARD ASSESSMENT OF THE ORGANOPHOSPHATES

REPORT OF THE

*H*AZARD *I*DENTIFICATION *A*SSESSMENT *R*EVIEW *C*OMMITTEE

HAZARD IDENTIFICATION ASSESSMENT REVIEW COMMITTEE

HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS
U.S. ENVIRONMENTAL PROTECTION AGENCY

July 7 , 1998

Committee Members in Attendance

Members present were: Karl Baetcke, William Burnam, Steven Dapson (for Sue Makris), Karen Hamernik, Robert Fricke, Nancy McCarroll, Michael Metzger (Co-Chairman), Melba Morrow, John Redden, Jess Rowland (Executive Secretary) and Clark Swentzel (Chairman),

HED staff (non-members) who participated in this reassessment were: Kathleen Raffaele of Toxicology Branch 2 and William Sette of Science Analysis Branch.

FQPA Safety Committee members in attendance (as observers) were Ray Kent and Brenda Tarplee (Executive Secretary)

Report Preparation: _____

Jess Rowland
Executive Secretary

TABLE OF CONTENTS

ATTACHMENTS

I. INTRODUCTION

The Hazard Identification Assessment Review Committee (HIARC) convened on May 12, 13 and 14, 1998 for a comprehensive review of 40 Organophosphates which were reviewed by this Committee during September 97 thru May 1998. HIARC's objective for this reassessment was to evaluate the following factors for consistency: 1) assessment of the neurotoxicity studies for evidence of neuropathology; 2) quantitative and qualitative assessment of the developmental and reproductive toxicity studies for enhanced susceptibility to infants and children as required by FQPA; 3) use of literature data in hazard identification; 4) identification of data gaps; 5) the criteria used in requiring a developmental neurotoxicity study; 6) recommendations on FQPA Safety Factor to the FQPA Safety Committee; 7) the toxicological endpoints and doses selected for acute and chronic dietary as well as occupational and residential exposure risk assessments; 8) selection of the dermal absorption factors for dermal risk assessments; and 9) application of FIFRA-related Uncertainty Factors.

The toxicology database was evaluated for the neurotoxic, developmental and reproductive toxic potential of the 40 organophosphates. Of the 40, the data base was inadequate for Chlorpyrifos methyl, Dicrotophos and Temephos and no data were available for Fonophos, Isazophos and Sulfotepp.

In order to maintain consistency, determination of susceptibility was performed for each pesticide on a case-by-case basis by always employing a weight-of-the evidence assessment. The two primary concerns or factors that contributed to the decision making process were: 1) enhanced **susceptibility** of the developing organism or offspring as observed in the prenatal developmental toxicity studies in rodents and non-rodents, and the multi-generation reproduction studies in rodents in conjunction with the rest of the toxicity data base; as well as evidence of neuropathology seen in the hen and rat neurotoxicity studies and other neuropathological findings (e.g., decreases in brain weights), which might be indicative of enhanced susceptibility of the developing nervous system and 2) **uncertainty** related to the absence of a complete data base (e.g., neurotoxicity studies in hen and/or rats) for the assessment of potential effects on infants and children. The HIARC did not consider these two factors to be separate distinct entities, but rather, they represented two aspects of an information continuum that defined the uncertainties in the scientific knowledge of the effects of any pesticide on the human population. Thus in recommending the FQPA Safety Factor, an evaluation of uncertainty and the susceptibility issues may be altered by weight-of-the-evidence considerations. This could include such factors as: the severity of toxic effects on the offspring; the presence of confounding factors such as severe maternal toxicity; a characterization of the dose response curve for effects related to offspring; concordance of treatment-related effects between species and/or strains; data or knowledge of mode of action; and the level of confidence in the data base or critical studies.

II. EVALUATION OF NEUROTOXICITY

The neurotoxicity data requirements include an acute delayed neurotoxicity study in hens, an acute neurotoxicity study in rats and a subchronic neurotoxicity study in rats.

The acute delayed neurotoxicity study in hens was evaluated for organophosphate induced delayed neurotoxicity (OPIDN), neurochemical assessment of inhibition of acetylcholinesterase and neurotoxic esterase (NTE) and histopathological assessment of brain, peripheral nerve, and spinal cord. The acute and the subchronic neurotoxicity studies in rats were usually evaluated for cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology of the central and peripheral nervous system following single (acute) or repeated (subchronic) exposures.

All of the organophosphates are neurotoxic in that they may cause cholinesterase inhibition and related clinical signs, up to and including death following exposure. Organophosphates also may cause neuropathology of the visual system or effects on cognitive function, i.e. learning and memory as well as other effects on the nervous system. While the acute and subchronic neurotoxicity studies might show some gross effects on the visual system or sensory function, these and other effects were not systematically evaluated at this meeting since the cause/effect relationship between cholinesterase inhibition and visual system effects has not been verified.

Of the 33 organophosphates evaluated, evidence of neuropathology was seen for the following:

CHEMICAL	EVIDENCE OF NEUROPATHOLOGY
CHLORPYRIFOS	Published studies have reported OPIDN in humans and animals (at lethal doses) and there have been case reports that indicate possible correlation of neurophysiological effects in humans.
METHAMIDOPHOS	Positive neurotoxic esterase in a subchronic toxicity study in hens and delayed peripheral neuropathy in humans as well as polyneuropathy in hens at extremely high dose levels (greatly in excess of the hen LD_{50}) reported in published studies.
METHYL PARATHION	Neuropathology in acute and subchronic neurotoxicity studies in rats as well as in the chronic toxicity studies in rats.
NALED	In an acute delayed neurotoxicity study, axonal degeneration of the spinal cord was seen following a single oral dose. However, no neuropathy was seen after repeated dosing in the subchronic neurotoxicity study in hens. No evidence of neuropathology was seen following single or repeated dosing in rats.
ODM	Evidence of neuropathology was seen in hens following a single dose but no neuropathology was seen following repeated dose in hens. No evidence of neuropathology was seen following single or repeated dosing in rats.
TRIBUFOS	Evidence of OPIDN and neuropathology following repeated dermal applications in a subchronic delayed neurotoxicity study in hens

CHEMICAL	EVIDENCE OF NEUROPATHOLOGY
TRICHLORFON	Evidence of OPIDN and neuropathology in the acute delayed neurotoxicity study in hens and neuropathology in the subchronic neurotoxicity study in hens.

A study that evaluates the effects on the NTE is required for the following chemicals. The lack of NTE data in an otherwise acceptable negative hen study is not considered a major data gap but rather characterized as the need for confirmatory data (i.e., data to confirm that an effect on NTE does not occur)::

ORGANOPHOSPHATES THAT REQUIRE ASSESSMENT OF NTE				
AZINPHOS METHYL	CADUSAFOS (1)	COUMAPHOS	DIMETHOATE	DISULFOTON (1)
ETHION	ETHOPROP	FENITROTHION	FENAMIPHOS	ISOFENFOS
METHIDATHION	METHYL PARATHION	PHORATE	PHOSTEBUPIRIM	PIRMIMIPHOS METHYL (1)
PROFENFOS	PROPETAMPHOS	TERBUFOS	TETRACHLOR-VINPHOS	TRIBUFOS
TRICHLORFON	(1) Data gap exists for an acute delayed neurotoxicity study for these four chemicals.			

III. DETERMINATION OF SUSCEPTIBILITY

The HIARC evaluated enhanced susceptibility of fetuses as compared to maternal animals following *in utero* exposure in rats and rabbits as well as the enhanced susceptibility of pups as compared to adults in the two generation toxicity study in rats. For most of the organophosphates, following *in utero* exposures, developmental effects were observed at or above treatment levels which resulted in evidence of maternal toxicity. Following pre and/or post natal exposure in the two-generation reproduction toxicity study, in general, effects in the offspring were most often manifested as decreased pup viability at doses that caused considerable inhibition of cholinesterase activity and cholinergic signs in the parental animals. Since the effects seen in the offspring (e.g., decreased pup viability) are confounded by the presence of maternal toxicity, it is difficult to regard the offspring effects as indicative of developmental toxicity or enhanced susceptibility of young animals. In addition, in the prenatal developmental toxicity studies, the parameters evaluated are not comparable between the dams and the fetuses. While the dams are routinely evaluated for survival, clinical signs, body weight, body weight gain and food consumption and certain reproductive parameters during the cesarian section, the fetuses undergo much more critical and more detailed evaluation. The primary effect for the organophosphates is the inhibition of cholinesterase activity. For most of the pesticides, however, comparative cholinesterase inhibition data for the dams and the pups were not available, thus precluding an evaluation of susceptibility based on this endpoint. When these

data (i.e., comparative cholinesterase) were available, however, no evidence of enhanced susceptibility was seen in the pups as compared to maternal animals (i.e., cholinesterase inhibition occurred at the same doses in the pups and parental animals).

1. <u>Prenatal Developmental Toxicity Study in Rats</u>

(a) The NOELs, LOELs and endpoints selected for maternal and developmental toxicity in the prenatal developmental toxicity studies in rats are provided in **Attachment 1**. No evidence of enhanced susceptibility was observed for 33 of 40 organophosphates following *in utero* exposure to pregnant rats. For these chemicals, there was no evidence of effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses. Of the remaining 7, an acceptable prenatal developmental toxicity study in rats was not available for Chlorpyrifos methyl, Dicrotophos, Temephos and Trichlorfon, and no data were available for Fonophos, Isazophos and Sulfotepp. It is noted that in pre/postnatal studies published in the open literature, evidence of enhanced susceptibility was demonstrated in rats for Chlorpyrifos following oral, subcutaneous and intraperitoneal administration and for Methyl Parathion via the subcutaneous and intraperitoneal routes.

(b) For four chemicals (tabulated below), the NOELs and LOELs were the same for maternal and developmental toxicity (i.e., fetal effects were seen at the same dose that caused maternal toxicity) but the developmental (fetal) effects appeared to be more severe. Following a qualitative evaluation of the effects observed, the HIARC concluded that fetal effects occurred at dose levels causing similar or more severe maternal toxicity. The rationale for this conclusion is provided for each chemical.

DEVELOPMENTAL TOXICITY SEEN IN THE PRESENCE OF MATERNAL TOXICITY	
CADUSAFOS	Decreased fetal body weights occurred at levels causing cholinergic signs in the dams characterized as tremors, muscle fasciculations, exophthalmus and decreased activity.
FENTHION	Increased post implantation losses were not accompanied by decreased litter sizes and no developmental effects were seen in the other parameters examined. Dams exhibited clinical signs and decreased body weights at the same dose that induced fetal effects. In addition, plasma, erythrocyte and brain cholinesterase inhibition was seen in dams at doses lower than those causing fetal effects indicating that the dams were under "stress".
FENITROTHION	At the dose that caused severe maternal toxicity characterized as tremors and decreases in body weight and body weight gains, there was an increased incidence of fetuses with skeletal variation.
TERBUFOS	The biological significance of the fetal effects (increases in early fetal resorptions and postimplantation losses) are questionable since similar effects (i.e., decreased litter size) were not seen in the two-generation study in rats. In addition, based on the results of other studies with this chemical, substantial cholinesterase inhibition may have occurred in dams (not measured in this study) and thus most likely contributed to the fetal effects.

2. <u>Prenatal Developmental Toxicity Study in Rabbits</u>

(a) The NOELs, LOELs and endpoints selected for the maternal and developmental toxicity in the prenatal developmental toxicity study in rabbits are provided in **Attachment 2.** No evidence of enhanced susceptibility was observed for 34 of 40 organophosphates following *in utero* exposure to pregnant rabbits. For these chemicals, there was no evidence of effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses Of the remaining 6, an acceptable prenatal developmental toxicity study in rabbits was not available for Chlorpyrifos methyl, Dicrotophos and Temephos, and no data was available for Fonophos, Isazophos and Sulfotepp.

(b) For five chemicals (tabulated below), the NOELs and LOELs were the same for maternal and developmental toxicity (i.e., fetal effects were seen at the same dose that caused maternal toxicity) but the developmental (fetal) effects appeared to be more severe. Following a qualitative evaluation of the effects observed, the HIARC concluded that fetal effects occurred at dose levels causing similar or more severe maternal toxicity. The rationale for this conclusion is provided for each chemical.

DEVELOPMENTAL TOXICITY SEEN IN THE PRESENCE OF MATERNAL TOXICITY	
CADUSAFOS	Severe maternal toxicity manifested as increased mortality and cholinergic signs at the same dose that caused an increase in total number of resorptions, decrease in total number of fetuses and fetal death.
ETHYL PARATHION	The same dose that caused maternal deaths, increased moribundity as well as decreases in body weight and body weight gains also caused a decrease in litter size.
MALATHION	The slight increase in mean resorption sites was not accompanied by alteration in litter size and occurred at the same doses that caused decreased maternal body weights.
PHOSMET	The dose that induced clinical signs and decreased body weight in dams also resulted in skeletal variations observed in the fetuses .
PROPETAMPHOS	The increased resorptions were not accompanied by decreases in litter size.

3. <u>Two-Generation Reproduction Study in Rats</u>

(a) The NOELs, LOELs and endpoints selected for the parental systemic and offspring toxicity in the two-generation reproduction study is provided in **Attachment 3.** No evidence of enhanced susceptibility was observed for 35 of 40 organophosphates following pre and/or post natal exposure in the two-generation reproduction study in rats (i.e., effects noted in offspring occurred at maternally toxic doses or higher). Of the remaining 5, an acceptable reproduction toxicity study in rats was not available for Chlorpyrifos methyl, and Temephos and no data were available for Fonophos, Isazophos and Sulfotepp.

(b) For the following chemicals, the NOELs and LOELs were same for parental systemic toxicity and offspring toxicity (i.e., offspring effects were seen at the same dose that caused parental effects) but the offspring (pup) effects appeared to be more severe. Following a qualitative evaluation of the effects observed, the HIARC concluded that the effects in the pups occurred at dose levels causing similar or more severe parental systemic toxicity. The rationale for this conclusion is provided for each chemical.

OFFSPRING TOXICITY SEEN IN THE PRESENCE OF PARENTAL TOXICITY	
ACEPHATE	Decreased viability index and decreased pup body weight gain were seen at the same dose that caused parental toxicity characterized by clinical signs (alopecia and soft stools) and decreased body weight gain. Although the clinical signs in parental animals are not severe, comparison to other studies (subchronic) indicated that cholinesterase inhibition (not measured in this study) would have occurred in dams at the dose that caused offspring toxicity and thus most likely contributed to offspring toxicity. Also, the offspring effects were seen in the first generation only and not repeated in the second generation (i.e., not a consistent finding).
DICHLORVOS	The abnormal estrous cycles observed in maternal animals most likely contributed to the offspring effects (reduced dams bearing litters, decreases in fertility and pregnant indices) observed at the same dose.
DIAZINON	Cholinesterase inhibition (ChEI) has occurred at lower doses with this chemical in other toxicity studies. ChEI was not measured in parental animals in the reproduction study. Therefore it is postulated that ChEI occurred in the maternal animals at the same doses causing pup mortality and decreased pup weight gain observed during lactation at which time the pup were exposed to the chemical via the milk.
FENITROTHION	The dose that caused severe parental systemic toxicity (decreases in body weight and body weight gain as well as food consumption) was also associated with offspring toxicity (decreases in fertility index, number of implantation sites and viability) in one generation. However, similar offspring toxicity was not seen in the second generation (i.e., not replicated in the second generation).

OFFSPRING TOXICITY SEEN IN THE PRESENCE OF PARENTAL TOXICITY	
ISOFENPHOS	Offspring toxicity manifested as increased pup mortality (reductions in lactation indices and mean litter size) and clinical signs (small to very small emaciated pups) were observed at the same dose that caused parental systemic toxicity (inhibition of plasma, erythrocyte and brain cholinesterase). The offspring toxicity was not considered to be more severe since 1) the effects were observed only after postnatal Day 14 and not on other days (i.e., a single occurrence) and thus the biological significance is not known; 2) during that period (i.e., later portion of lactation), young rats consume approximately twice the diet per unit body weight as an adult rat consumes. Estimation of the test substance intake in pre-weaning animals is likely to be more than double the adult intake because of the availability of the test material both via the milk (lactation) and food, particularly after the mid point of lactation. and 3) the dose that caused the offspring toxicity also caused cholinesterase inhibition (all three compartments) in parental animals.
MALATHION	The decreases in the F1a and F2b pup body weight occurred at a lower dose than the dose that caused parental toxicity; this was not a true indication of enhanced susceptibility because: 1) pup body weight decrements were primarily observed at postnatal Day 21; 2) during that period, young rats consume approximately twice the diet per unit body weight as an adult rat consumes; and 3) the estimation of the test substance intake in pre-weaning animals is likely to be more than double the adult intake because of the availability of the test material both via the milk (lactation) and food, particularly after the mid point of lactation.
METHAMIDAPHOS	Substantial cholinesterase inhibition was seen at lower doses in other toxicity studies conducted with rats indicating that cholinesterase inhibition most likely occurred in parental animals at the dose that caused offspring toxicity (decreased pup viability). Also this effect was seen only on postnatal Day 14 and only in one generation. It is noted that decreased pup viability was also seen with Acephate, a related organophosphate, at the same dose that caused parental toxicity.
ODM	The same dose that caused cholinesterase inhibition in parental animals also caused the offspring toxicity (decreased viability index, decreased litter size at birth and decreased pup body weight gain during lactation). In addition, no enhanced susceptibility was seen in adults vs. fetuses based on comparative cholinesterase inhibition data (i.e., cholinesterase inhibition occurred at the same doses in the pups and the parental animals).

OFFSPRING TOXICITY SEEN IN THE PRESENCE OF PARENTAL TOXICITY	
PHORATE	The same dose that caused severe parental toxicity (tremors and inhibition of plasma and brain cholinesterase activity) also caused decreased pup survival and pup body weight.

IV. SUMMARY OF FQPA ASSESSMENT

CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
1) ACEPHATE	OPIDN: Negative Neuropathology: Negative NTE: Negative <u>Literature Data</u> NTE: Positive	Neuropathology: Negative Cholinesterase activity measured (ChEI):Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	None
2) AZINPHOS METHYL	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	None
3) BENSULIDE	OPIDN: Negative NTE: Negative	Neuropathology: Negative ChEI measured: Yes	Study Waived	No increased Susceptibility	No increased Susceptibility	Not Required	None

CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
4) CADUSAFOS	Inadequate Study (No histopathology or NTE data) Confirmatory NTE Study Required	Not available	Not available	No increased Susceptibility	No increased Susceptibility	**Reserved** Pending Acute Hen, Acute & 90-day rat neurotoxicity studies	Acute-Hen Acute -Rat Neurotoxicity 90-Day -Rat Neurotoxicity
		No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology					
5) CHLOR-ETHOXYFOS	OPIDN: Negative Neuropathology: Negative	Neuropathology: Negative ChEI measured: Yes	Waived since other studies showed no evidence of neuropathology	No increased Susceptibility	No increased Susceptibility	Not Required	None
6) CHLORPYRIFOS	OPIDN: Negative <u>Literature Data</u> OPIDN: Positive NTE: Positive	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility <u>Literature Data</u> Enhanced susceptibility seen in young rats (ChEI, behavioral and other developmental neurotoxic effects).	No increased Susceptibility	**Required** Literature Data OPIDN: Positive	Develop-mental Neurotoxicity Study in Rats

CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
7) CHLORPYRIFOS METHYL	Equivocal evidence of neuropathology	Not available	Not available	Studies Unacceptable To Assess Susceptibility	Study Unacceptable To Assess Susceptibility	Can Not Be Ascertained Due to Inadequate Data Base	Acute Rat 90-Day Rat Neurotoxicity Develop-mental -Rat & Rabbit 2-Generation Reproduction
		No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology					
8) COUMAPHOS	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Not available	Not available	No increased Susceptibility	No increased Susceptibility	**Reserved** Pending Acute & 90-day neurotoxicity studies	Acute - Rat 90-Day-Rat
9) DDVP	<u>Acute</u> OPIDN: Equivocal <u>28-day</u> Neuropathology: Negative NTE: Negative	Neuropathology Negative ChEI measured: Yes	Neuropathology Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	**Reserved** Pending results of developmental toxicity study in Guinea Pigs requested by HIARC. See HIARC Report.	None

CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
10) DIAZINON	OPIDN: Negative Neuropathology: Negative NTE: Negative	Neuropathology Negative ChEI measured: Yes	Neuropathology Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	None
11) DICROTOPHOS	Unacceptable study	Neuropathology: Negative	Neuropathology Negative	FQPA ASSESSMENT COULD NOT BE MADE DUE TO INADEQUATE DATA BASE			
12) DIMETHOATE	OPIDN: Negative Neuropathology: Negative NTE: Equivocal Confirmatory NTE study Required	Neuropathology: Negative ChEI measured: No.	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	None
13) DISULFOTON	Unacceptable Study	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Equivocal ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	**Reserved** Pending Acute Hen study	Acute Hen

CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
14) ETHION	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Neuropathology: Negative ChEI measured: No	Equivocal neuropathology at high dose ChEI measured: No	No increased Susceptibility	No increased Susceptibility	Not required	None
15) ETHOPROP	OPIDN: Negative Neuropathology: Negative NTE requested by RfD Committee 5/96	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	None
16) ETHYL PARATHION	OPIDN: Negative NTE : Negative Neuropathology: Negative	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	None
17) FENAMIPHOS	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not required	None

CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
18) FENITROTHION	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Neuropathology: Negative ChEI measured: No	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not required	None
19) FENTHION	<u>Acute (Oral & Dermal)</u> OPIDN: Negative Neuropathology: Negative NTE: Negative <u>Subchronic</u> OPIDN: Negative Neuropathology: Negative	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	No Required	None
20) FONOFOS	NO DATA AVAILABLE						

CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
21) ISOFENPHOS	<u>Acute</u> OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required <u>Subchronic</u> OPIDN: Negative Neuropathology: Negative	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	None
22) TRIUMPH (ISAZOPHOS)	**NO DATA AVAILABLE**						
23) MALATHION	OPIDN: Negative Neuropathology: Negative **<u>Literature Data</u>** NTE:-Negative	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not required	None

CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
24) METHA-MIDOPHOS	Acute & Subchronic OPIDN: Negative Neuropathology: Negative NTE: Negative (Acute) Positive (subchronic) *Racemate & Enantiomers* **Positive** for OPIDN at extremely high levels **Literature Data** Polyneuropathy & peripheral neuropathy in humans at high doses. Polyneuropathy in adult hens at high doses	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	**Required** Positive NTE Polyneuropathy in hens and Delayed peripheral neuropathy in humans in published studies	Develop-mental Neurotoxicity Study in Rats

CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
25) METHIDATHION	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Neuropathology: Negative ChEI measured: Yes	Negative for neuropathology ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not required	None
26) METHYL PARATHION	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	**Positive** for neuropathology ChEI measured: Yes	**Equivocal** for neuropathology ChEI measured: Yes	No increased Susceptibility in Subdivision F studies. **<u>Literature Data</u>** **Qualitative evidence of increased Susceptibility seen in open literature rat studies via subcutaneous. & intraperitoneal routes at high doses.**	No increased Susceptibility	**Required** Positive neuropathology in acute rat Equivocal neuropathology in subchronic rat Positive Neuropathology in Chronic Rat and 1-Year Rat	Develop-mental Neurotoxicity Study in Rats

CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
27) NALED	<u>Acute</u> OPIDN: Positive Neuropathology: Positive NTE: Negative <u>Subchronic</u> OPIDN: Negative	Neuropathology: Negative ChEI measured: No	Neuropathology: Negative ChEI measured: No	No increased Susceptibility	No increased Susceptibility	Not Required	None
28) ODM	<u>Acute</u> Neuropathology: Positive Confirmatory NTE Study Required <u>Subchronic</u> Neuropathology: Negative	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	Mouse Specific Locus Test.

CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
29) PHORATE	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required.	Not available	Not available	No increased Susceptibility	No increased Susceptibility	**Reserved** Pending Acute & 90-day rat neurotoxicity studies	Acute-Rat Neurotoxicity 90-day Rat Neurotoxicity
		No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology					
30) PHOSMET	OPIDN: Negative Neuropathology: Negative NTE: Negative Need re-review	Not available	Not available	No increased Susceptibility	No increased Susceptibility	**Reserved** Pending Acute & 90-day rat neurotoxicity studies & Confirmation of results of hen studies	Acute-Rat Neurotoxicity 90-day Rat Neurotoxicity
		No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology					
31) PHOSTE-BUPIRIM	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Not available	Not available	No increased Susceptibility	No increased Susceptibility	**Reserved** Pending Acute & 90-day rat neurotoxicity studies	Acute-Rat Neurotoxicity 90-day Rat Neurotoxicity
		No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology					

CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
32) PIRIMIPHOS-METHYL	No Acute study Subchronic: Unacceptable	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	**Reserved** Pending Acute Hen & Chronic Dog/Rat	Acute-Hen Chronic Toxicity-Dog Chronic Toxicity-Rat
33) PROFENFOS	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Neuropathology: Negative ChEI measured: Yes	Neuropathology: Negative ChEI measured: Yes	No increased Susceptibility	No increased Susceptibility	Not Required	None
34) PROPETAMPHOS	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Neuropathology: Negative ChEI measured: No	Neuropathology: Negative ChEI measured: No	No increased Susceptibility	No increased Susceptibility	Not Required	None
35) SULFOTEPP	**NO DATA AVAILABLE - INADEQUATE DATA BASE**						

CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
36) TEMEPHOS	Study Unacceptable Confirmatory NTE Study Required	Not available	Not available	There are no food uses for this chemical thus requiring only a minimal data base. However, both the oral and dermal developmental toxicity study in rats as well as a three generation reproduction study in rats are unacceptable. Thus, an adequate assessment for FQPA can not be made with the existing database.			
37) TERBUFOS	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Not available	Not available	No increased Susceptibility	No increased Susceptibility	**Reserved** Pending Acute & 90-day rat neurotoxicity studies	Acute-Rat Neurotoxicity 90-day Rat Neurotoxicity
		No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology					
38) TETRACHLOR-VINPHOS	OPIDN: Negative Neuropathology: Negative Confirmatory NTE Study Required	Neuropathology: Negative ChEI measured: No	Neuropathology: Negative ChEI measured: No	No increased Susceptibility	No increased Susceptibility	Not required	None

CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
39) TRIBUFOS	<u>Subchronic Dermal</u> OPIDN: Positive Neuropathology: Positive Confirmatory NTE Study Required	Not available	Not available	No increased Susceptibility	No increased Susceptibility	**Required** Evidence of neuropathology in the subchronic hen study	Acute -Hen (subchronic is via the dermal route). Acute - Rat Neurotoxicity 90-day - Rat Neurotoxicity Develop-mental Neurotoxicity Study in Rats
		No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology					

CHEMICAL	ACUTE DELAYED NEUROTOXICITY HEN	MAMMALIAN NEUROTOXICITY - RAT		EVIDENCE OF ENHANCED SUSCEPTIBILITY IN DEVELOPMENTAL STUDIES RAT & RABBIT	EVIDENCE OF ENHANCED SUSCEPTIBILITY IN THE 2-GENERATION REPRODUCTION RAT	REQUIREMENT OF A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS	DATA GAPS
		ACUTE	SUBCHRONIC				
40) TRICHLORFON	<u>Acute</u> OPIDN: Positive Neuropathology: Positive Confirmatory NTE Study Required <u>Subchronic</u> OPIDN: Negative Neuropathology: Positive	Not available	In Review	No increased Susceptibility (Rabbit) **Rat (unacceptable)**	No increased Susceptibility	**Reserved** 1)Pending results of the developmental toxicity study in Guinea Pig required by HIARC. 2) Receipt and review of the Developmental toxicity study in rats	Acute-Rat Neurotoxicity 90-day Rat Neurotoxicity Develop-mental Toxicity -Rat
		No data to assess neurotoxicity, cholinesterase inhibition, behavioral effects, or neuropathology					

V. HIARC's RECOMMENDATIONS FOR THE FQPA SAFETY FACTOR COMMITTEE.

The toxicology database was evaluated for the neurotoxic, developmental and reproductive toxic potential of the 40 organophosphates. The data base was inadequate for Chlorpyrifos methyl, Dichrotophos and Temephos. No data were available for Fonophos, Isazophos and Sulfotepp. For one chemical (Dichlorvos or DDVP), the FQPA Safety Factor was determined by the Division Directors. Thus, HIARC's recommendation of the FQPA Safety Factor to the FQPA Safety Committee for 33 organophosphates are presented below:

1. Recommendation to the FQPA Safety Committe for *REMOVAL* of the additional 10 x Factor Based on Hazard Alone

The HIARC, based on hazard assessment, recommends, that the additional **10 x factor** for enhanced susceptibility of infants and children should be **removed** for the organophosphates listed below based on the following weight-of-the-evidence considerations:

(a) In prenatal developmental toxicity studies following *in utero* exposure in rats and rabbits, there was no evidence of effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses.

(b) In the pre/post natal two-generation reproduction study in rats, there was no evidence of enhanced susceptibility in pup when compared to adults (i.e., effects noted in offspring occurred at maternally toxic doses or higher)..

(c) There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies. .

(d) There was no convincing evidence for requiring a developmental neurotoxicity study in rats.

(e) The toxicology data base is complete and there are no data gaps according to Subdivision F Guideline requirements including meeting any of the triggers for requiring a developmental neurotoxicity study in rats.

ORGANOPHOSPHATES FOR WHICH THE 10 X FACTOR SHOULD BE REMOVED		
ACEPHATE	AZINPHOS METHYL	BENSULIDE[(1)]
CHLORETHOXYFOS[(2)]	DIAZINON	DIMETHOATE
ETHION	ETHOPROP	ETHYL PARATHION
FENAMIPHOS	FENTHION	FENITROTHION
ISOFENFOS	MALATHION	METHIDATHION
NALED[(3)]	PROFENFOS	PROPETAMPHOS
TETRACHLORVINPHOS		

[(1)] Bensulide: The HIARC determined that the absence of a subchronic neurotoxicity study in rats alone does not warrant retaining or reducing the FQPA Safety Factor because neuropathology was not observed either in the acute delayed neurotoxicity study in hen or in the acute neurotoxicity study in rats or any other studies. This chemical will be re-evaluated upon receipt and evaluation of the subchronic neurotoxicity study.

[(2)] Chlorethoxyfos: The requirement for a subchonic neurotoxicity study in rats was waived because several other studies in the data base provided adequate evidence for the absence of neuropathology. Therefore, this is not considered to be a data gap requiring a FQPA Safety Factor.

[(3)] Naled: The acute delayed neurotoxicity study in hens revealed neurotoxicity (clinical signs and brain cholinesterase inhibition) and neuropathology (axonal degeneration of the spinal cord). These effects, however, were not seen following repeated dosing in the subchronic neurotoxicity study in hens. Also, there was no evidence of neuropathology in rats following single and multiple exposures and there was no evidence of enhanced susceptibility following *in utero* exposures in rats and rabbits as well as pre and/or post natal exposures in the two generation reproduction study in rats. Based on these weight-of-the-evidence considerations, it is recommended that the FQPA Safety Factor can be removed for this chemical

2. Recommendation to the FQPA Safety Committe for *REDUCTION* of the additional 10 x Factor Based on Hazard Alone

The FQPA requires that an additional 10 x margin of safety be applied for infants and children to take into account the potential pre-and postnatal toxicity and the completeness of the data with respect to exposure and toxicity.

For the organophosphates, in general, the neurotoxicity data requirement include an acute delayed neurotoxicity study in hens (§81-7), an acute neurotoxicity study in rats (§81-8) and a subchronic neurotoxicity study in rats (§82-5).[Reference: OMB 2070-0107; 5/8/91].

Data from these studies are used for hazard characterization as well as in determining the need for a developmental neurotoxicity study. The "trigger" for a developmental

neurotoxicity study for example, will be "positive" histopathology in these studies as well as central nervous system effects (e.g., decrease in brain weights) in these or other toxicology studies (e.g., 90-day or chronic studies). When a developmental neurotoxicity study is required, it is because this study will provide additional data (e.g., functional parameter development, potential increased susceptibility, effects on the development of the fetal nervous system, etc.). When the requirement for a developmental neurotoxicity study is placed in reserve status, the Agency will make the final requirement decision following evaluation of the results of the neurotoxicity studies (i.e., datagaps).

For the organophosphates listed below, the neurotoxicology data base is not considered to be incomplete since none of them are missing all three neurotoxicity studies. Two are missing the hen study but have the rat studies while five are missing the rat studies but have the hen study. Thus, the lack of a "complete" data base for these chemicals requires an FQPA Safety Factor. The HIARC, however, recommends that the **10 x factor** can be **reduced (to be determined)** and this recommendation is based on the following weight-of-the-evidence considerations:

(a) In prenatal developmental toxicity studies following *in utero* exposure in rats and rabbits, there was no evidence of effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses.

(b) In the pre/post natal two-generation reproduction study in rats, there was no evidence of enhanced susceptibility in pup when compared to adults (i.e., effects noted in offspring occurred at maternally toxic doses or higher).

(c) There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies.

(d) There is no concern for positive neurological effects from the available neurotoxicity studies or for histopathology in the central nervous system from the other toxicological studies (e.g., subchronic rat, chronic dog, chronic mouse and rat).

(e) The doses selected for dietary and non-dietary exposure risk assessments are based on the most sensitive endpoint (cholinesterase inhibition) occurring at low dose levels (0.005 to 1.1 mg/kg/day).

(f) The dose level selected for acute dietary exposure risk assessments are from multiple dosing regimen.

(g) Historical experience shows that neuropathology appears at higher doses relative to cholinesterase inhibition (the endpoint that is currently used for risk assessments).

The HIARC determined that the "missing" neurotoxicity studies for these organophosphates are necessary for completion of hazard characterization as well as to confirm the doses that are currently used for risk assessment/regulatory purposes are fully protected.

If the neurotoxicity studies provide no evidence of neuropathology and/or there was no convincing evidence for requiring a developmental neurotoxicity study, then HIARC would recommend that the FQPA Safet Factor (yet to be determined) be removed for these organophosphates based on hazard alone. However, until that decisions can be made, HIARC considers the lack of neurotoxicity studies as datagaps thus requiring an FQPA Safety Factor.

The Table below is a summary of the specific studies that are missing in the toxicology data base. However, all of the weight-of-the-evidence considerations discussed above also apply (e.g., lack of enhanced susceptibility in the critical developmetnatl and reproduction toxicity studies etc.,). Therefore, the Committee considers the reduction of the FQPA Safety Factor to be an appropriate recommendation.

CHEMICAL	**RATIONALE FOR REDUCING THE FQPA SAFETY FACTOR (UNDETERMINED)**
PIRIMIPHOS METHYL	1) Data gap for an Acute Delayed Neurotoxicity Study in Hen, Chronic toxicity studies in dogs and rats. 2) No evidence of neuropathology in rats following single or repeated exposures. 3) The requirement for a Developmental Neurotoxicity Study in Rats placed in *Reserve* status pending receipt of acute delayed neurotoxicity study in hens.
DISULFOTON	1) Data gap for Acute Delayed Neurotoxicity Study in Hen 2) Equivocal evidence of neuropathology in the Subchronic Neurotoxicity Study in Rats. 3) The requirement for a Developmental Neurotoxicity Study in Rats placed in *Reserve* status pending receipt and review of a repeated acute delayed neurotoxicity study in hens.
COUMAPHOS	1) Negative for OPIDN and neuropathology; a NTE study required as confirmatory data. 2) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats. 3) Therefore, data on cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology of the central and peripheral nervous system were not available for evaluation following single (acute) or repeated (subchronic) exposures to Coumophos. 4) The requirement for a Developmental Neurotoxicity Study in Rats placed in *Reserve* status pending receipt and review of the acute and subchronic neurotoxicity studies.

CHEMICAL	RATIONALE FOR REDUCING THE FQPA SAFETY FACTOR (UNDETERMINED)
PHORATE	1) Negative for OPIDN and neuropathology; a NTE study is required as confirmatory data. 2) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats. 3) Therefore, data on cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology of the central and peripheral nervous system were not available for evaluation following single (acute) or repeated (subchronic) exposures to Phorate. 4) The requirement for a Developmental Neurotoxicity Study in Rats placed in *Reserve* status pending receipt and review of the acute and subchronic neurotoxicity studies.
PHOSMET	1) Negative for OPIDN and neuropathology; a NTE study is required as confirmatory data. 2) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats. 3) Therefore, data on cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology of the central and peripheral nervous system were not available for evaluation following single (acute) or repeated (subchronic) exposures to Phosmet. 4) The requirement for a Developmental Neurotoxicity Study in Rats placed in *Reserve* status pending receipt and review of the acute and subchronic neurotoxicity studies.
PHOSTEBUPIRIM	1) Negative for OPIDN and neuropathology; a NTE study is required as confirmatory data. 2) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats. 3) Therefore, data on cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology of the central and peripheral nervous system were not available for evaluation following single (acute) or repeated (subchronic) exposures to Phostebupirim. 4) The requirement for a Developmental Neurotoxicity Study in Rats placed in *Reserve* status pending receipt and review of the acute and subchronic neurotoxicity studies.
TERBUFOS	1) Negative for OPIDN and neuropathology; a NTE study is required as confirmatory data. 2) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats. 3) Therefore, data on cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology of the central and peripheral nervous system were not available for evaluation following single (acute) or repeated (subchronic) exposures to Terbufos. 4) The requirement for a Developmental Neurotoxicity Study in Rats placed in *Reserve* status pending receipt and review of the acute and subchronic neurotoxicity studies.

CHEMICAL	RATIONALE FOR REDUCING THE FQPA SAFETY FACTOR (UNDETERMINED)
METHAMIDAPHOS	1) Evidence of positive effects in the NTE assay in hens in Subchronic Toxicity Studies.. 2)In studies from *open literature*, ingestion of Methamidaphos has been shown to result in delayed peripheral neuropathy in humans. Similarly, adult hens developed poly neuropathy but only after ingestion of doses 12-16 times the LD_{50}. 3) The HIARC recognized that the dose levels causing delayed neuropathy in humans are NOT well characterized. Exposures occurred at high doses through accidental occupational poisoning, suicide attempts or ingestion of contaminated vegetables. 4) Based on this evidence, a Developmental Neurotoxicity Study in Rats is **required**

3. Recommendation to the FQPA Safety Committe for *RETAINING* the additional 10 x Factor Based on Hazard Alone

The HIARC, based on hazard assessment, recommends that the additional **10 x factor** for enhanced susceptibility of infants and children should be **retained** for the organophosphates listed below. The rational for this recommendation is provided in the table.

CHEMICAL	RATIONALE FOR RETAINING THE 10 X FQPA SAFETY FACTOR
CADUSAFOS	1) Data gap for Acute Delayed Neurotoxicity Study in Hen as well as Acute and Subchronic Neurotoxicity Studies in Rats. 2) Therefore, data on organophosphate induced delayed neurotoxicity (OPIDN), NTE and neuropathology in hens as well as cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology of the central and peripheral nervous system in rats were not available for evaluation following single (acute) or repeated (subchronic) exposures to Cadusofos. 3) The requirement for a Developmental Neurotoxicity Study in Rats placed in *Reserve* status pending receipt and review of the acute delayed neurotoxicity study in hens as well as the acute and subchronic neurotoxicity studies in rats.
CHLORPYRIFOS	1) Chlorpyrifos is a neurotoxicant with evidence of OPIDN in humans and animals; there have been case reports of neurophysiological effects in humans. 2) In studies (published/unpublished) conducted in various reputable scientific research laboratories and reported in the open literature, increased susceptibility of offspring to the effects of Chlorpyrifos has been identified. 3) A Developmental Neurotoxicity Study in Rats is **required** and thus there are data gaps for the assessment of functional development of young animals following pre- and/or postnatal exposure.

CHEMICAL	RATIONALE FOR RETAINING THE 10 X FQPA SAFETY FACTOR
METHYL PARATHION	1) Evidence of neuropathology in acute and subchronic neurotoxicity studies in rats as well as in the chronic toxicity studies in rats. 2) In studies (published) conducted in various reputable scientific research laboratories and reported in the open literature, qualitative evidence of enhanced susceptibility to perinatal rats has been identified following subcutaneous and intraperitoneal administration at high doses. 3) The HIARC noted that open literature data for another organophosphate, chlorpyrifos has also demonstrated differences in susceptibility in the offspring following oral, subcutaneous and intraperitoneal administrations. 4) Even though these routes of exposure (i.e., subcutaneous and intraperitoneal) are not the traditional (i.e., oral), enhanced susceptibility was seen in studies published in the open literature and also, neuropathology was seen in two chronic studies in rats submitted to the Agency. Therefore, based on these considerations, a Developmental Neurotoxicity Study in Rats is **required**.
ODM	Concern for possible adverse heritable effects based in the *in vivo* mouse spot test which was positive for the induction of somatic cell mutations following prenatal administration. Also, there was clear evidence of DNA strand breaks in rat testes cells in an *in vitro* alkaline elution assay (not confirmed *in vivo*). Based on this, HIARC recommended a mouse specific locus test.
TRIBUFOS	1) Evidence of OPIDN and neuropathology in hens following repeated dermal applications in a Subchronic Delayed Neurotoxicity Study. 2) Data gap for Acute Delayed Neurotoxicity Study in Hen Acute and Subchronic Neurotoxicity Studies in Rats. 3) Therefore, data on OPIDN and neuropathology in hens as well as cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology of the central and peripheral nervous system in rats were not available for evaluation following single (acute) or repeated (subchronic) exposures to TRIBUFOS. 4) Ocular effects and neuropathology at low doses in various other studies. 5) Based on the neuropathology observed in the subchronic study, a Developmental Neurotoxicity Study in Rats is **required.**

CHEMICAL	RATIONALE FOR RETAINING THE 10 X FQPA SAFETY FACTOR
TRICHLORFON	1) Evidence of OPIDN and neuropathology in hens in the Acute Delayed Neurotoxicity Study. 2) Evidence of neuropathology in hens in the Subchronic Delayed Neurotoxicity Study.. 3) Data gap for Acute and Subchronic Neurotoxicity Studies in Rats. 4) Therefore, data on cholinesterase inhibition, neurobehavioral effects (FOB), and histopathology of the central and peripheral nervous system in rats were not available for evaluation following single (acute) or repeated (subchronic) exposures to Trichlorfon. 5) Data gap for a Prenatal Developmental Toxicity Study in Rats which precluded an assessment of susceptibility in rat fetuses as compared to maternal animals. 6) Open literature identified a developmental toxicity in Guinea Pigs in which oral administration of Triclorfon resulted in decreases in brain weights. 7) A Developmental Neurotoxicity Study in Rats is **reserved** pending the results of the prenatal developmental toxicity study in Guinea Pigs, acute and subchronic neurotoxicity studies in rats and a prenatal developmental toxicity study in rats.

VI. EVALUATION OF THE TOXICOLOGY ENDPOINTS SELECTION

The **toxicological endpoints selected** for the various exposure scenarios are provided **in Attachment 4.**. The **dose levels** selected for the various exposure risk assessments are provide in **Attachment 5.**

The conventional Uncertainty Factor (UF)of 100 (i.e., 10 x for intra-species variation and 10 x for inter-species extrapolation) is adequate for 25 of the 35 organophosphates evaluated. For the remaining 10, the HIARC applied an additional UF for various reasons. A re-evaluation found the rationale that was used in the application of the additional UF's to be consistent. The 10 chemicals for which the additional UF's were applied are tabulated below:

The use of additional Uncertainty Factors for Toxicology Endpoints Selected

CHEMICAL NAME	EXPOSURE SCENARIO	UF	RATIONALE FOR USE OF ADDITOINAL UNCERTAINTY FACTOR
AZINPHOS METHYL	Acute Dietary	3	Use of a LOEL in the critical (acute neurotoxicity) study.
DIAZINON	Chronic Dietary, Residential, Short, Intermediate and Long-Term Dermal and Inhalation.	3	Closeness of the NOEL/LOEL and the use of one sex (males) in the critical (human) study..
ETHION	Chronic Dietary Residential, Short, Intermediate and Long-Term Dermal	10	Use of a LOEL for in the critical (human) study. Use of the human study with a LOEL and results of a 21-day dermal toxicity study in rabbits indicated that brain cholinesterase activity may be inhibited at lower doses than plasma and erythrocyte inhibition.
ETHYL PARATHION	Chronic Dietary	3	Use of a LOEL in the critical study (1-year dog).
FENAMIPHOS	Acute Dietary	3	Use of a LOEL in the critical (acute neurotoxicity) study.
FENTHION	Chronic Dietary	3	Use of threshold NOEL/LOE in the critical (monkey) and co-critical (human) studies
ISOFENPHOS	Acute Dietary, Residential, Short-Term Dermal and Inhalation	3	Use of a LOEL in the critical (acute neurotoxicity) study.
ODM	Acute Dietary Inhalation (any time period)	3	Use of a LOEL in the critical (acute neurotoxicity) study. Use of a LOEL in the critical study
PIRIMIPHOS METHYL	Chronic Dietary	30	Use of a LOEL in the critical (human) study (3x) as well as data gaps for chronic studies in dogs and rats (10x).
	Intermediate-Term Dermal	3	Use of a LOEL in the critical (human) study.
	Long-Term Dermal	30	Use of a LOEL in the critical (human) study (3x) as well as data gaps for chronic studies in dogs and rats (10x).
TRIBUFOS	Short and Intermediate-Term Dermal	10	Use of a LOEL in the critical (21-day dermal) study via the relevant route (dermal) of exposure.

During the evaluation, the HIARC identified and/or modified some of the toxicological endpoints selected previously by the Toxicology Endpoint Selection Committee (TESC). This was done (for a few chemicals) because doses and endpoints were not selected for certain exposure scenarios (e.g., Long-Term Dermal and/or Inhalation) by the TESC during the "initial-phase" of the TESC process. Modifications made at this meeting for 15 organophosphates are summarized below:

MODIFICATIONS MADE IN THE TOXICOLOGY ENDPOINT SELECION						
CHEMICAL NAME	**CHANGED PARAMETER**	**DOSES**		**END POINT**		**RATIONALE FOR CHANGE**
		PREVIOUS SELECTION	**CHANGED TO**	**PREVIOUS SELECTION**	**CHANGED TO**	
BENSULIDE	Dermal Absorption	None	100%	NA	NA	A dermal absorption study was not available, thus the default value was selected.
	Inhalation (Any Time Period)	LC50 = 1.75 mg/L	<u>Oral Equivalents</u> Short-Term: Oral NOEL=5.5 mg/kg/day Intermediate & Long-Term: Oral NOEL= 0.5 mg/kg/day	Clinical signs	Cholinesterase inhibition (ChEI).	Selected Oral NOELs since the dose selected previously by the Toxicology Endpoint Selection Committee (TESC) was an LC_{50} value which is not appropriate for use in risk assessments.
CHLOR-ETHOXYPHOS	Long-Term Dermal	None selected	Oral NOEL = 0.06 mg/kg/day with 100% Dermal absorption	None selected	CheI	A dose and endpoint was not selected for Long-Term dermal risk assessment. previously by the Toxicology Endpoint Selection Committee (TESC).
	Inhalation (Any Time Period)	None selected	<u>Oral Equivalents</u> Short-,Intermediate & Long-Term :Oral NOEL= 0.06 mg/kg/day	None selected	ChEI	A dose and endpoint for inhalation risk assessment was not selected previously by TESC.
COUMOPHOS	Inhalation (Any Time Period)	None selected	<u>Oral Equivalents</u> Short-& ,Intermediate: Oral NOEL= 0.2 mg/kg/day	None selected	ChEI	A dose and endpoint for inhalation risk assessment was not selected previously by TESC. Long-Term inhalation risk assessment is not required based on the use pattern.

MODIFICATIONS MADE IN THE TOXICOLOGY ENDPOINT SELECION						
CHEMICAL NAME	**CHANGED PARAMETER**	**DOSES**		**END POINT**		**RATIONALE FOR CHANGE**
		PREVIOUS SELECTION	**CHANGED TO**	**PREVIOUS SELECTION**	**CHANGED TO**	
DIMETHOATE	Acute Dietary	2.0 mg/kg/day	Oral NOEL = 0.06 mg/kg/day	Absence of pupil response in rats	ChEI	Lack of confidence in the previous endpoint (absence of pupil response) selected. Also, no ChEI measurement in the acute neurotoxicity study.
	Short-Term Dermal	2.0 mg/kg/day	Oral NOEL = 0.06 mg/kg/day with 11% dermal absorption.	Absence of pupil response in rats	ChEI	Lack of confidence in the previous endpoint selected (absence of pupil response) as well as lack of ChEI measurement in the acute neurotoxicity study.
	Inhalation (Any Time Period)	None selected	<u>Oral Equivalents</u> Short-and Intermediate Term: Oral NOEL=0.06 mg/kg/day Long-Term :Oral NOEL= 0.05 mg/kg/day	None selected	ChEI	A dose and endpoint for inhalation risk assessment was not selected previously by TESC.

MODIFICATIONS MADE IN THE TOXICOLOGY ENDPOINT SELECION						
CHEMICAL NAME	**CHANGED PARAMETER**	**DOSES**		**END POINT**		**RATIONALE FOR CHANGE**
		PREVIOUS SELECTION	**CHANGED TO**	**PREVIOUS SELECTION**	**CHANGED TO**	
ETHION	Long -Term Dermal	None selected	Oral LOEL=0.05 mg/kg/day	None selected	Clinical signs of ChEI.	A dose and endpoint for Long-Term dermal risk assessment was not selected previously by TESC. Human study with a LOEL is used, therefore a MOE of 100 is required..
	Inhalation (Any Time Period)	None selected	Oral Equivalents Short, Intermediate and long..- Term: Oral NOEL=0.05 mg/kg/day	None selected	Clinical signs of ChEI.	A dose and endpoint for inhalation exposure risk assessment was not selected previously by TESC. Human study with a LOEL is used, therefore a MOE of 100 is required..
ETHOPROP	Inhalation (Any Time Period)	None selected	Oral Equivalents Short Term: Oral NOEL = 0.025 mg/kg/day Intermediate and Long-Term: Oral NOEL =0.01 mg/kg/day	None selected	ChEI.	A dose and endpoint for inhalation exposure risk assessment was not selected previously by TESC

MODIFICATIONS MADE IN THE TOXICOLOGY ENDPOINT SELECION						
CHEMICAL NAME	**CHANGED PARAMETER**	**DOSES**		**END POINT**		**RATIONALE FOR CHANGE**
		PREVIOUS SELECTION	**CHANGED TO**	**PREVIOUS SELECTION**	**CHANGED TO**	
FENTHION	Inhalation (Any Time Period)	None selected	Oral Equivalents Short Term: Oral NOEL = 0.07 mg/kg/day Intermediate and Long-Term: Oral NOEL =0.02 mg/kg/day	None selected	ChEI.	A dose and endpoint for inhalation exposure risk assessment was not selected previously by TESC.
ISOFENPHOS	Long -Term Dermal	None selected	Oral NOEL=0.06 mg/kg/day	None selected	Clinical signs of ChEI.	A dose and endpoint for Long-Term dermal risk assessment was not selected previously by TESC.
METHA-MIDAPHOS	Short, Intermediate and Long- Term Dermal	Short-Term: Oral NOEL =0.14 mg/kg/day Intermediate & Long-Term: Oral NOEL=0.3 mg/kg/day with 100% dermal absorption.	Dermal NOEL = 1.0 mg/kg/day	ChEI	ChEI	A 21-day dermal toxicity study in rats became available since the HIARC meeting of 1/20/98 at which the oral NOELs were selected for dermal risk assessments.

MODIFICATIONS MADE IN THE TOXICOLOGY ENDPOINT SELECION						
CHEMICAL NAME	**CHANGED PARAMETER**	**DOSES**		**END POINT**		**RATIONALE FOR CHANGE**
		PREVIOUS SELECTION	**CHANGED TO**	**PREVIOUS SELECTION**	**CHANGED TO**	
METHIDATHION	Inhalation (Any Time Period)	None selected	Oral Equivalents Short-and Intermediate Term: Oral NOEL=0.2 mg/kg/day Long-Term: Oral NOEL= 0.15 mg/kg/day	None selected	ChEI	A dose and endpoint for inhalation risk assessment was not selected previously by TESC.
PHOSTEBUPIRIM	Long -Term Dermal	None selected	Oral NOEL=0.02 mg/kg/day	None selected	ChEI.	A dose and endpoint for Long-Term dermal risk assessment was not selected previously by TESC.
PROFENOPHOS	Dermal Absorption	50%	100% default	NA	NA	Previously the 50% dermal absorption was estimated based on LD_{50} values. The dermal absorption value was changed to 100% (default) to be consistent with other chemicals.
TERBUFOS	Long -Term Dermal	None selected	Oral NOEL=0.005 mg/kg/day	None selected	ChEI.	A dose and endpoint for Long-Term dermal risk assessment was not selected previously by TESC.

MODIFICATIONS MADE IN THE TOXICOLOGY ENDPOINT SELECION						
CHEMICAL NAME	**CHANGED PARAMETER**	**DOSES**		**END POINT**		**RATIONALE FOR CHANGE**
		PREVIOUS SELECTION	**CHANGED TO**	**PREVIOUS SELECTION**	**CHANGED TO**	
TETRACHLOR-VINPHOS	Acute dietary	None selected	Oral NOEL = 5.0 mg/kg/day	None selected	ChEI	A dose and endpoint for acute dietary risk assessment was not selected previously by TES.
	Short, Intermediate, and Long- Term Dermal	None selected	Short-and Intermediate Term: Oral NOEL =5.0 Long-Term: Oral NOEL= 4.23% with a dermal absorption factor of 9.57%	None selected	ChEI	A doses and endpoint for dermal risk assessment was not selected previously by TESC.
	Inhalation (Any Time Period	None selected	<u>Oral Equivalents</u> Short-and Intermediate Term: Oral NOEL=5.0 mg/kg/day Long-Term: Oral NOEL= 4.23 mg/kg/day	None selected	ChEI	A doses and endpoint for inhalation risk assessment was not selected previously by TESC.

MODIFICATIONS MADE IN THE TOXICOLOGY ENDPOINT SELECION						
CHEMICAL NAME	**CHANGED PARAMETER**	**DOSES**		**END POINT**		**RATIONALE FOR CHANGE**
		PREVIOUS SELECTION	**CHANGED TO**	**PREVIOUS SELECTION**	**CHANGED TO**	
TRICHLORFON	Dermal Absorption	None selected	10%	NA	NA	A dermal absorption factor was not required since doses and endpoints for dermal risk assessments were not selected previously by TESC. A 10% dermal absorption factor was derived by the ratio of the Oral LOEL of 35 mg/kg/day in the developmental toxicity study in rabbits and the Dermal LOEL of 300 mg/kg/day from the 21-day dermal toxicity study in rabbits.
	Short and, Intermediate-and Long -Term Dermal	Non selected None selected	Dermal NOEL=100 mg/kg/day Oral NOEL = 0.2 mg/kg/day with 10% dermal absorption.	None None	ChEI ChEI	A dose and endpoint for dermal risk assessment was not selected previously by TESC.
	Inhalation (Any Time Period)	None selected	Inhalation NOEL = 0.0127 mg/L	None	ChEI	A dose and endpoint for inhalation risk assessment was not selected previously by TESC.

VIII. CONCLUSIONS

HED's FQPA Safety Factor Committee met on June 15 -16, 1998 and considered the following recommendations made by the HIARC (based hazard alone) in conjunction with the dietary, drinking water and residential exposure assessments for each of these pesticides. A report from the FQPA Safety Factor Committee will be forthcoming which will include the final recommendations for the FQPA Safety Factors based on hazard and exposure assessments.

The HIARC's recommendations (based only on hazard assessment) to the FQPA Safety Committee are summarized below:

The FQPA Safety Factor can be **removed** for ***Acephate, Azinphos Methyl, Bensulide, Chlorethoxyfos' Diazinon, Dimethoate, Ethion, Ethoprop, Ethyl Parathion, Fenamiphos, Fenthion, Fenitrothion, Isofenfos, Malathion, Methidathion, Naled' Profenfos, Propetamphos and Tetrachlorvinphos*** since there was not evidence of enhances susceptibility in fetuses in the prenatal developmental toxicity studies in rodents and non rodents or in the pups in the two-generation reproduction study in rats and the toxicology data base is complete.

The FQPA Safety Factor can be **reduced (value undetermined):** For ***Coumophos, Dichlorvos, DISULFOTON, Phorate, Phomet, Phostebupirim, Pirimiphos methyl, and Terbufos*** due to datagaps for acute hen, acute rat and/or subchronic rat neurotoxicity studies as well as placement of the developmental neurotoxicity study in *Reserve* status pending receipt and review of the preceding studies. For ***Methamidaphos,*** however, the FQPA Safety Factor can be **reduced** (to be determined) due to evidence of neurotoxicity in hens, occurrence of delayed peripheral neuropathy in humans, and the requirement for a developmental neurotoxicity study. The HIARC, however, noted that the dose at which neuropathology occurred in humans was probably high and is not well characterized.

The FQPA Safety Factor should be **retained** for: ***Cadusafos*** because of datagaps for three studies (acute hen, acute rat and subchronic rat neurotoxicity); for ***Chlorpyrifos*** **and** ***Methyl parathion*** due to evidence of neuropathology as well enhanced susceptibility from the open literature studies and thus the need for a developmental neurotoxicity study; for ***ODM*** because for the concern for heritable effects and the requirement for a mouse specific locust test; for ***Tribufos*** due to evidence of OPIDN and neuropathology in hens via the dermal route, ocular effects and neuropathology in several species, datagaps for the acute and subchronic neurotoxicity studies in rats as well as the requirement for a developmental neurotoxicity study; for ***Trichlorfon*** because of evidence of OPIDN and neuropathology in hens, datagaps for acute and subchronic neurotoxicity as well as a prenatal developmental toxicity study in rats and the placement of the developmental neurotoxicity study in rats in reserve status pending the results of the developmental toxicity study in the guinea pigs.

No recommendations of the FQPA Safety Factor are made for Chlorpyrifos methyl, Dicrotophos, Fonophos, Isazophos, and Sulfotepp due to the inadequate toxicology data base and/or absence of data to evaluate the potential enhanced susceptibility to infants and children.

Attachment 5. FQPA Safety Factor Recommendations for the Organophosphates (A Combined Report of the Hazard Identification Assessment Review Committee and the FQPA Safety Factor Committee).

FQPA SAFETY FACTOR RECOMMENDATIONS FOR THE ORGANOPHOSPHATES

A Combined Report of the
Hazard Identification Assessment Review Committee and the
FQPA Safety Factor Committee

HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS
U.S. ENVIRONMENTAL PROTECTION AGENCY

August 6, 1998

Committee Members in Attendance

Members present were: William Burnam, Richard Kiegwin, Ray Kent, Deborah McCall, Kathy Monk, Daniel Rieder, Jess Rowland, Brenda Tarplee (Executive Secretary), Edward Zager (Chairperson)**.**

Hazard Identification Assessment Review Committee member present as observer: Susan Makris.

Report Preparation: _____

Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee

_____

Jess Rowland, Executive Secretary
Hazard Identification Assessment Review Committee

06-AUG-1998

MEMORANDUM

SUBJECT: ***FQPA SAFETY FACTOR RECOMMENDATIONS FOR THE ORGANOPHOSPHATES*** (A Combined Report of the Hazard Identification Assessment Review Committee and the FQPA Safety Factor Committee)

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)
and
Jess Rowland, Executive Secretary
Hazard Identification Assessment Review Committee

Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Margaret Stasikowski, Division Director
Health Effects Division (7509C)

Attached is a combined report of HED's Hazard Identification Assessment Review Committee (HIARC) and the FQPA Safety Factor Committee. This report includes the data presented in the July 7, 1998 Report of the HIARC, as well as the recommendations made by the FQPA Safety Factor Committee.

I. INTRODUCTION

The Hazard Identification Assessment Review Committee (HIARC) convened on May 12 - 14, 1998 for a comprehensive review of 40 Organophosphates which were originally reviewed by this Committee from September 1997 through May 1998.

The FQPA Safety Factor Committee (FQPA SFC) met on June 15 and 16, 1998 to evaluate hazard and exposure data for the organophosphates and to determine whether the data on each organophosphate are sufficiently reliable to permit reduction or removal of the 10-fold safety factor mandated by the Food Quality Protection Act of 1996 to protect infants and children from exposure to pesticides.

This report includes the results of both Committee meetings, including the recommendations for the FQPA safety factor (by the FQPA SFC) and a listing of additional uncertainty factors (by the HIARC) for use in the risk assessment process for the organophosphates.

II. HAZARD ASSESSMENT

HIARC's objective for this reassessment was to evaluate the following factors for consistency: 1) assessment of neurotoxicity studies for evidence of neuropathology; 2) quantitative and qualitative assessment of developmental and reproductive toxicity studies for enhanced susceptibility of infants and children as required by FQPA; 3) use of literature data in hazard identification; 4) identification of data gaps; 5) criteria used in triggering a developmental neurotoxicity study; 6) recommendations on FQPA Safety Factor to the FQPA Safety Committee; 7) the toxicological endpoints and doses for acute and chronic dietary as well as occupational and residential exposure risk assessments; 8) selection of dermal absorption factors for dermal risk assessments; and 9) application of FIFRA-related uncertainty factors.

Determination of susceptibility was performed for each pesticide on a case-by-case basis employing a weight-of-evidence assessment. The two primary concerns or factors that contributed to the decision-making process were: 1) enhanced **susceptibility** of the developing organism or offspring as might be observed in prenatal developmental toxicity studies in rodents and non-rodents, as well as multi-generation reproduction studies in rodents. The entire toxicity data base; particularly the hen and rat neurotoxicity studies, was evaluated for evidence of neuropathology (e.g., decreases in brain weights), which might be indicative of increased susceptibility of the developing nervous system; and 2) **uncertainty** related to the absence of complete toxicity data for the assessment of potential effects on infants and children.

The HIARC did not consider these two factors to be separate entities, but rather aspects of an information continuum that defined the uncertainties in how pesticides might affect humans.

Thus in recommending an FQPA Safety Factor, an evaluation of susceptibility and uncertainty

issues might be altered by weight-of-evidence considerations such as: the severity of toxic effects in offspring in comparison to severity of maternal effects; a characterization of the dose-response
curve for effects related to offspring; concordance of treatment-related effects between species and/or strains; knowledge of mode of action; and the level of confidence in the data base or critical studies.

The toxicology data base was evaluated for the neurotoxic, developmental and reproductive toxic potential of the 40 organophosphates. Of the 40, the data base was inadequate for Chlorpyrifos-methyl, Dicrotophos, and Temephos and no data were available for Fonofos, Isazophos, and Sulfotepp.

1. <u>Evaluation of Neurotoxicity</u>

The neurotoxicity data requirements include an acute delayed neurotoxicity study in hens, an acute neurotoxicity study in rats, and a subchronic neurotoxicity study in rats.

The acute delayed neurotoxicity study in hens was evaluated for organophosphate-induced delayed neurotoxicity (OPIDN); assessment of inhibition of acetylcholinesterase; and neurotoxic esterase (NTE); and histopathological assessment of brain, peripheral nerve, and spinal cord. Acute and the subchronic neurotoxicity studies in rats were usually evaluated for cholinesterase inhibition; neurobehavioral effects (Functional Observational Battery); and histopathology of the central and peripheral nervous system following single or repeated exposures.

All of the organophosphates are neurotoxic in that they may cause cholinesterase inhibition and related clinical signs, up to and including death following exposure. Organophosphates also may cause neuropathology of the visual system or effects on cognitive function, i.e., learning and memory as well as other effects on the nervous system. While acute and subchronic neurotoxicity studies may show some gross effects on the visual system or sensory function, these and other effects were not systematically evaluated at this meeting since the cause and effect relationship between cholinesterase inhibition and visual system effects has not been verified.

Of the 34 organophosphates that had neurotoxicity studies available, evidence of neuropathology was seen for the following:

CHEMICAL	EVIDENCE OF NEUROPATHOLOGY
Chlorpyrifos	Published studies have reported OPIDN in humans and animals (at lethal doses) and there have been case reports that indicate possible correlation of neurophysiological effects in humans.
Methamidophos	Positive neurotoxic esterase in a subchronic toxicity study in hens and delayed peripheral neuropathy in humans as well as polyneuropathy in hens at extremely high dose levels (greatly in excess of the hen LD_{50}) reported in published studies.
Methyl Parathion	Neuropathology in acute and subchronic neurotoxicity studies in rats and the chronic toxicity studies in rats.
Naled	In an acute delayed neurotoxicity study, axonal degeneration of the spinal cord was seen following a single oral dose. However, no neuropathy was seen after repeated dosing in the subchronic neurotoxicity study in hens. No evidence of neuropathology was seen following single or repeated dosing in rats.
ODM	Evidence of neuropathology was seen in hens following a single dose but no neuropathology was seen following repeated dose in hens. No evidence of neuropathology was seen following single or repeated dosing in rats.
Tribuphos	Evidence of OPIDN and neuropathology following repeated dermal applications in a subchronic delayed neurotoxicity study in hens.
Trichlorfon	Evidence of OPIDN and neuropathology in the acute delayed neurotoxicity study in hens and neuropathology in the subchronic neurotoxicity study in hens.

A study that evaluates the effects on the NTE is necessary for the following chemicals. The lack of NTE data in an otherwise acceptable negative hen study is not considered a major data gap, but indicates a need for confirmatory data (i.e., data to confirm that an effect on NTE does not occur).

ORGANOPHOSPHATES THAT REQUIRE ASSESSMENT OF NTE

Azinphos-Methyl Ethion Methidathion Profenophos Trichlorfon	Cadusafos[1] Ethoprop Methyl Parathion Propetamphos	Coumaphos Fenitrothion Phorate Terbufos	Dimethoate Fenamiphos Phostebupirim Tetrachlorvinphos	Disulfuton[1] Isofenphos Pirimiphos-Methyl[1] Tribuphos

[1] Data gap exists for an acute delayed neurotoxicity study for these four chemicals.

2. Determination of Susceptibility

The HIARC evaluated the potential for enhanced susceptibility from exposure to these pesticides as required by the FQPA. This evaluation entailed the enhanced susceptibility of fetuses as compared to maternal animals following *in utero* exposure in rats and rabbits, as well as the enhanced susceptibility of pups as compared to adults in the two-generation toxicity study in rats. For most of these pesticides, following *in utero* exposures, developmental effects were observed at or above treatment levels which resulted in evidence of maternal toxicity. Following pre- and/or postnatal exposure in the two-generation reproduction toxicity study, in general, effects in the offspring were most often manifested as decreased pup viability at doses that caused considerable inhibition of
cholinesterase activity and cholinergic signs in the parental animals. Since the effects seen in the offspring (e.g., decreased pup viability) are confounded by the presence of maternal toxicity, it is difficult to regard the offspring effects as indicative of developmental toxicity or enhanced susceptibility of young animals. In addition, in the prenatal developmental toxicity studies, the parameters evaluated are not comparable between the dams and the fetuses. While the dams are routinely evaluated for survival, clinical signs, body weight, body weight gain, food consumption, and certain reproductive parameters during the cesarian section, the fetuses undergo much more critical and more detailed evaluation. Therefore, the HIARC conducted a qualitative evaluation of the effects seen in the fetuses and/or pups as compared to the maternal/parental effects in order to ascertain whether the fetal/offspring effects were true indicators of susceptibility.

The primary effect for the organophosphates is the inhibition of cholinesterase activity. For most of the pesticides, however, comparative cholinesterase inhibition data for the dams and the pups were not available, thus precluding an evaluation of susceptibility based on this endpoint. When these data (i.e., comparative cholinesterase) were available however, no evidence of enhanced susceptibility was seen in the pups as compared to maternal animals (i.e., cholinesterase inhibition occurred at the same doses in the pups and parental animals).

i. Prenatal Developmental Toxicity Study in Rats

(a) The NOELs, LOELs, and endpoints selected for maternal and developmental toxicity in the prenatal developmental toxicity studies in rats are provided in **Attachment 1**. No evidence of enhanced susceptibility was observed for 33 of 40 organophosphates following *in utero* exposure to pregnant rats. For these chemicals, there was no evidence of developmental effects being produced in fetuses at lower doses as compared to maternal animals, nor was there evidence of an increase in severity of effects at or below maternally toxic doses. Of the remaining 7: an acceptable prenatal developmental toxicity study in rats was not available for Chlorpyrifos-methyl, Dicrotophos, Temephos, and Trichlorfon; and no data were available for Fonofos, Isazophos, and Sulfotepp. It is noted that in pre/postnatal studies published in the open literature, evidence of enhanced susceptibility was demonstrated in rats for Chlorpyrifos following oral, subcutaneous and intraperitoneal administration and for Methyl Parathion via the subcutaneous, and intraperitoneal routes.

(b) For four chemicals (tabulated below), the NOELs and LOELs were the same for maternal and developmental toxicity (i.e., fetal effects were seen at the same dose that caused maternal toxicity) but the developmental (fetal) effects initially appeared to be more severe. Following a qualitative re-evaluation of the effects observed, the HIARC concluded that fetal effects occurred at dose levels causing similar or more severe maternal toxicity. The rationale for this conclusion is provided for each chemical.

DEVELOPMENTAL TOXICITY IN THE PRESENCE OF MATERNAL TOXICITY (DEVELOPMENTAL TOXICITY STUDIES-RATS)	
Cadusafos	Decreased fetal body weights occurred at levels causing cholinergic signs in the dams characterized as tremors, muscle fasciculations, exophthalmus and decreased activity.
Fenthion	Increased post-implantation losses were not accompanied by decreased litter sizes and no developmental effects were seen in the other parameters examined. Dams exhibited clinical signs and decreased body weights at the same dose that induced fetal effects. In addition, plasma, erythrocyte, and brain cholinesterase inhibition was seen in dams at doses lower than those causing fetal effects indicating that the dams were under stress.
Fenitrothion	There was an increased incidence of fetuses with skeletal variations at a dose that caused severe maternal toxicity, characterized as tremors and decreases in body weight and body weight gains.

DEVELOPMENTAL TOXICITY IN THE PRESENCE OF MATERNAL TOXICITY (DEVELOPMENTAL TOXICITY STUDIES-RATS)	
Terbufos	The biological significance of the fetal effects (increases in early fetal resorptions and postimplantation losses) are questionable since similar effects (i.e., decreased litter size) were not seen in the two-generation study in rats. In addition, based on the results of other studies with this chemical, substantial cholinesterase inhibition may have occurred in dams (not measured in this study) and thus most likely contributed to the fetal effects.

ii. <u>Prenatal Developmental Toxicity Study in Rabbits</u>

(a) The NOELs, LOELs, and endpoints selected for the maternal and developmental toxicity in the prenatal developmental toxicity study in rabbits are provided in **Attachment 2.** No evidence of enhanced susceptibility was observed for 34 of 40 organophosphates following *in utero* exposure to pregnant rabbits. For these chemicals, there was no evidence of developmental effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses. Of the remaining 6, an acceptable prenatal developmental toxicity study in rabbits was not available for Chlorpyrifos-methyl, Dicrotophos, and Temephos, and no data was available for Fonofos, Isazophos, and Sulfotepp.

(b) For five chemicals (tabulated below), the NOELs and LOELs were the same for maternal and developmental toxicity (i.e., fetal effects were seen at the same dose that caused maternal toxicity) but the developmental (fetal) effects appeared to be more severe. Following a qualitative evaluation of the effects observed, the HIARC concluded that fetal effects occurred at dose levels causing similar or more severe maternal toxicity. The rationale for this conclusion is provided for each chemical.

DEVELOPMENTAL TOXICITY IN THE PRESENCE OF MATERNAL TOXICITY (DEVELOPMENTAL TOXICITY STUDIES-RABBITS)	
Cadusafos	Severe maternal toxicity manifested as increased mortality and cholinergic signs at the same dose that caused an increase in total number of resorptions, decrease in total number of fetuses, and fetal death.
Ethyl Parathion	The dose that caused maternal deaths, increased moribundity, as well as decreases in body weight and body weight gains also caused a decrease in litter size.
Malathion	The slight increase in mean resorption sites was not accompanied by alteration in litter size and occurred at the same doses that caused decreased maternal body weights.
Phosmet	The dose that induced clinical signs and decreased body weight in dams, also resulted in skeletal variations observed in the fetuses.
Propetamphos	The increased resorptions were not accompanied by decreases in litter size.

iii. <u>Two-Generation Reproduction Study in Rats</u>

(a) The NOELs, LOELs, and endpoints selected for the parental systemic and offspring toxicity in the two-generation reproduction study is provided in **Attachment 3.** No evidence of enhanced susceptibility was observed for 35 of 40 organophosphates following pre and/or post natal exposure in the two-generation reproduction study in rats (i.e., effects noted in offspring occurred at maternally toxic doses or higher). Of the remaining 5, an acceptable reproduction toxicity study in rats was not available for Chlorpyrifos-methyl, and Temephos, and no data were available for Fonofos, Isazophos, and Sulfotepp.

(b) For the following chemicals, the NOELs and LOELs were same for parental systemic toxicity and offspring toxicity (i.e., offspring effects were seen at the same dose that caused parental effects) but the offspring (pup) effects initially appeared to be more severe. Following a qualitative reevaluation of the effects observed, the HIARC concluded that the effects in the pups occurred at dose levels causing similar or more severe parental systemic toxicity. The rationale for this conclusion is provided for each chemical.

OFFSPRING TOXICITY IN THE PRESENCE OF PARENTAL TOXICITY (MULTIGENERATION REPRODUCTION TOXICITY STUDIES-RATS)	
Acephate	Decreased viability index and decreased pup body weight gain were seen at the same dose that caused parental toxicity characterized by clinical signs (alopecia and soft stools) and decreased body weight gain. Although the clinical signs in parental animals are not severe, comparison to other studies (subchronic) indicated that cholinesterase inhibition (not measured in this study) would have occurred in dams at the dose that caused offspring toxicity and thus most likely contributed to offspring toxicity. Also, the offspring effects were seen in the first generation only and not repeated in the second generation (i.e., not a consistent finding).
Dichlorvos	The abnormal estrous cycles observed in maternal animals most likely contributed to the offspring effects (reduced dams bearing litters, decreases in fertility and pregnancy indices) observed at the same dose.
Diazinon	Cholinesterase inhibition (ChEI) was not measure in parental animals in the reproduction study. ChEI was, however, was observed at lower doses in the other toxicity studies. Therefore it is postulated that ChEI occurred in the maternal animals at the same doses causing pup mortality and decreased pup weight gain observed during lactation at which time the pups were exposed to the chemical via the milk.

OFFSPRING TOXICITY IN THE PRESENCE OF PARENTAL TOXICITY (MULTIGENERATION REPRODUCTION TOXICITY STUDIES-RATS)	
Fenitrothion	The dose that caused severe parental systemic toxicity (decreases in body weight and body weight gain as well as food consumption) was also associated with offspring toxicity (decreases in fertility index, number of implantation sites and viability) in one generation. However, similar offspring toxicity was not seen in the second generation (i.e., not replicated in the second generation).
Isofenphos	Offspring toxicity manifested as increased pup mortality (reductions in lactation indices and mean litter size) and clinical signs (small to very small emaciated pups) were observed at the same dose that caused parental systemic toxicity (inhibition of plasma, erythrocyte and brain cholinesterase). The offspring toxicity was not considered to be more severe since: 1) the effects were observed only after postnatal Day 14 and not on other days (i.e., a single occurrence) and thus the biological significance is not known; 2) during that period (i.e., later portion of lactation), young rats consume approximately twice the diet per unit body weight as an adult rat consumes. Estimation of the test substance intake in pre-weaning animals is likely to be more than double the adult intake because of the availability of the test material both via the milk (lactation) and food, particularly after the mid point of lactation; and 3) the dose that caused the offspring toxicity also caused cholinesterase inhibition (all three compartments) in parental animals.
Malathion	The decreases in the F1a and F2b pup body weight occurred at a lower dose than the dose that caused parental toxicity; this was not a true indication of enhanced susceptibility because: 1) pup body weight decrements were primarily observed at postnatal Day 21; 2) during that period, young rats consume approximately twice the diet per unit body weight as an adult rat consumes; and 3) the estimation of the test substance intake in pre-weaning animals is likely to be more than double the adult intake because of the availability of the test material both via the milk (lactation) and food, particularly after the mid point of lactation.

OFFSPRING TOXICITY IN THE PRESENCE OF PARENTAL TOXICITY (MULTIGENERATION REPRODUCTION TOXICITY STUDIES-RATS)	
Methamidophos	Substantial cholinesterase inhibition was seen at lower doses in other toxicity studies conducted with rats indicating that cholinesterase inhibition most likely occurred in parental animals at a dose that caused offspring toxicity (decreased pup viability). Also this effect was seen only on postnatal Day 14 and only in one generation. It is noted that decreased pup viability was also seen with Acephate, a related organophosphate, at the same dose that caused parental toxicity.
Oxydemeton-methyl (ODM)	The same dose that caused cholinesterase inhibition in parental animals also caused offspring toxicity (decreased viability index, decreased litter size at birth, and decreased pup body weight gain during lactation). In addition, no enhanced susceptibility was seen in adults vs. fetuses based on comparative cholinesterase inhibition data (i.e., cholinesterase inhibition occurred at the same doses in the pups and the parental animals).
Phorate	The same dose that caused severe parental toxicity (tremors and inhibition of plasma and brain cholinesterase activity) also caused decreased pup survival and pup body weight.

3. Summary of the Hazard Assessments

The HIARC's assessments for neurotoxicity, enhanced susceptibility, the need for additional data, or the requirement of a developmental neurotoxicity study is summarized in **Attachment 4**.

III. EXPOSURE ASSESSMENT

1. Dietary Exposure

i. Considerations

Dietary exposure assessment addresses the potential for exposure to infants and children from pesticide residues in food. Considerations include: the evaluation of use patterns; actual dietary consumption and exposure data or estimates; and the completeness of the data, including characterization of uncertainties pertaining to dietary exposure.

For each pesticide, the following information was evaluated (as available):

- Whether the pesticide has major agricultural uses.
- Range of application rates and frequency of applications.

- Range of established tolerances and the nature of the metabolites requiring regulation.
- Whether the pesticide is used on commodities preferentially consumed by infants and children (such as citrus fruit, pome fruit, cereal grains, milk, soybeans, etc.); and if so, which ones.
- Whether the pesticide is "systemic", indicating residues are distributed throughout the commodity and not likely to be removed by preparation such as washing or peeling.
- Available residue data sources for the pesticide (field studies, FDA monitoring data, PDP monitoring data, etc.).
- Brief description of the range and frequency of positive residue findings for the pesticide.
- Extent of possible refinement to the Dietary Risk Evaluation System (DRES) analyses (ie., tolerance levels, anticipated residues (ARs), percent crop treated (%CT), monitoring data, Monte Carlo distributional analysis, etc.).

ii. Summary of Dietary Exposure Assessments

A summary table of the considerations used in the dietary exposure assessments for each of the OPs is presented in **Attachment 5**. This information was obtained from the HED Reregistration Eligibility Document (RED) Chapters or executive summaries of the HED RED Chapter, Dietary Risk Evaluation System (DRES) analyses reports, and/or risk characterization summaries.

2. Drinking Water Exposure

i. Considerations

Drinking water exposure assessment addresses the potential for exposure to infants and children from contaminated water sources. Considerations include: actual exposure data or estimates; the completeness of the environmental fate data, including characterization of uncertainties, as well as the evaluation of the use patterns pertaining to drinking water exposure.

For each pesticide, the following information was evaluated (as available):

- Completeness of the environmental fate data base.
- Whether the compound or its degradate(s) has the potential to leach to drinking water sources.
- Whether ground and/or surface water studies (or other appropriate, reliable, targeted monitoring data) were used to calculate estimated environmental concentrations (EECs) for the pesticide; and if so, whether the studies were conducted in vulnerable areas at maximum label rates.
- Whether ground water and surface water EECs were based on modeling; and if so, the model and tier used.

- Description of the extent of exposure and the potential population affected.

ii. Summary of Drinking Water Exposure Assessments

A summary table of the considerations used in the drinking water exposure assessments for each of the OPs is presented in **Attachment 6**. This information was obtained from the HED Reregistration Eligibility Document (RED) Chapters or executive summaries of the HED RED Chapter, EFED Drinking Water Assessment reports, and/or risk characterization summaries.

3. Residential Exposure

i. Considerations

Residential exposure assessment addresses the potential for exposure to infants and children from non-dietary, non-occupational sources. Considerations include: the evaluation of use patterns; actual exposure data or estimates; and the completeness of the data, including characterization of uncertainties pertaining to residential exposure.

For each pesticide, the following information was evaluated (as available):

- Whether infants and children could be exposed from the use of the pesticide.
- Whether pesticide-specific or site-specific data are available for the exposure assessment.
- Whether Pesticide Handler Exposure Data base (PHED) data is used; and if so, whether the scenarios used reflect the actual use pattern.
- Whether the *Draft Standard Operating Procedures for Residential Exposure Assessments* were used as the basis for post-application exposure calculations; and if so, a description of any deviations from SOP calculations.
- Whether other models were used; and if so, the model and tier used.
- Whether any biological exposure or epidemiology data are available (e.g., incident reports, CDC monitoring data, etc.); and if so, a description of the data.
- Whether 100% dermal absorption is assumed in the exposure assessment when dermal endpoints are derived from oral studies.

ii. Summary of Residential Exposure Assessments

A summary table of the considerations used in the residential exposure assessments for each of the OPs is presented in **Attachment 7.** This information was obtained from the HED Reregistration Eligibility Document (RED) Chapters or executive summaries of the HED RED Chapter, and/or risk characterization summaries.

IV. FQPA SAFETY FACTOR RECOMMENDATION AND RATIONALE

In determining whether to recommend removal, reduction, or retention of the FQPA safety factor for each of the organophosphates, the Committee considered: 1) the hazard and dose response evaluations; 2) the exposure assessment(s); and 3) the characterization of both the hazard and exposure data base.

1. Recommendations for the FQPA Safety Factor

The FQPA Safety Factors recommended by the FQPA Safety Factor Committee are presented below:

Removed (1x)	Reduced to 3x	Retained (10x)
Acephate Azinphos-methyl Bensulide Chlorethoxyfos Diazinon Dimethoate Ethion Ethoprop Ethyl Parathion Fenamiphos Fenitrothion Fenthion Malathion Methidathion Naled Profenofos Propetamphos Tetrachlorvinphos	Coumaphos Dichlorvos (DDVP) Disulfoton Isofenphos Methamidophos Phorate Phosmet Phostebupirim Pirimiphos-methyl Terbufos	Cadusafos Chlorpyrifos Methyl parathion Oxydemeton-methyl Tribuphos (DEF) Trichlorfon

Retained (10x) - Inadequate Tox Data base	Other
Chlorpyrifos-methyl Dicrotophos Temephos	Fonofos: cancellation proceedings are in place. Isazophos-methyl: no toxicology or exposure data are available for an adequate assessment. Sulfotepp: FQPA not applicable (greenhouse use only).

2. Rationale for the Recommendations for the FQPA Safety Factor

i. FQPA Safety Factor Removed (1x)

For **Acephate, Azinphos-methyl, Bensulide, Chlorethoxyfos, Diazinon, Dimethoate, Ethion, Ethoprop, Ethyl Parathion, Fenamiphos, Fenthion, Fenitrothion, Malathion, Methidathion, Naled, Profenofos, Propetamphos, and Tetrachlorvinphos** the FQPA safety factor is **removed** based on the following factors:

(a) In prenatal developmental toxicity studies following *in utero* exposure in rats and rabbits, there was no evidence of developmental effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses.

(b) In the pre/post natal two-generation reproduction study in rats, there was no evidence of enhanced susceptibility in pup when compared to adults (i.e., effects noted in offspring occurred at maternally toxic doses or higher).

(c) There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies.

(d) There is no concern for positive neurological effects from the available neurotoxicity studies or for histopathology in the central nervous system from the other toxicological studies (e.g., subchronic rat, chronic dog, chronic mouse and rat).

(e) The toxicology data base is complete and there are no data gaps according to the Subdivision F Guideline requirements.

(f) Adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess dietary and residential exposure and to provide a screening level drinking water exposure assessment.

ii. FQPA Safety Factor Reduced (3x)

For **Coumaphos, Dichlorvos, Disulfoton, Isofenphos, Methamidophos, Phorate, Phosmet, Phostebupirim, Pirimiphos-methyl, and Terbufos** the FQPA safety factor is **reduced to 3x.**

In general, the hazard (based on the neurotoxicity, developmental and reproductive toxicity studies) and exposure (dietary, drinking water and residential) assessments for these ten pesticides indicate the following:

(a) In prenatal developmental toxicity studies following *in utero* exposure in rats and rabbits, there was no evidence of developmental effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses.

(b) In the pre/post natal two-generation reproduction study in rats, there was no evidence of enhanced susceptibility in pups when compared to adults (i.e., effects noted in offspring occurred at maternally toxic doses or higher).

(c) There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies.

(d) There is no concern for positive neurological effects from the available neurotoxicity studies or for histopathology in the central nervous system from the other toxicological studies (e.g., subchronic rat, chronic dog, chronic mouse and rat studies).

(e) Adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess dietary and residential exposure and to provide a screening level drinking water exposure assessment.

However, there were partial data gaps for the neurotoxicity studies (7 pesticides) and evidence of neuropathology (2 pesticides) which led to either requiring or reserving the requirement for a developmental neurotoxicity study for these pesticides (9 total). When a developmental neurotoxicity study is required, it is because this study will provide additional data (e.g., potential increased susceptibility, effects on the development of the fetal nervous system, etc.). When the requirement for a developmental neurotoxicity study is placed in reserve status, the Agency will make the final requirement decision following evaluation of the results of the neurotoxicity studies (i.e., data gaps). For one pesticide there was concern for decreased brain weights in guinea pig fetuses as reported in the open literature, as well as uncertainty in the chemical specific residential exposure data.

Therefore, the Committee determined that a FQPA safety factor was necessary for these pesticides. However, it was determined that the 10x factor can be reduced to 3 x and the rationale is provided below:

Specifically, for **Coumaphos, Disulfoton, Phorate, Phosmet, Phostebupirim, Pirimiphos-methyl, and Terbufos** the FQPA safety factor is **reduced to 3x** because of data gaps for one of the neurotoxicity studies (i.e., acute delayed neurotoxicity-hen and/or acute or subchronic-rat) and the requirement for a developmental neurotoxicity study placed in reserve status. The results of these neurotoxicity studies may “trigger” the requirement of a developmental neurotoxicity study which in turn will provide additional data (e.g., potential increased susceptibility, effects on the development of the fetal nervous system, etc.).

For **Methamidophos** and **Isofenphos** there was evidence of neuropathology reported in the open literature indicating that an FQPA safety factor is appropriate. The Committee, however, determined that the 10x factor can be **reduced** to **3x** because: 1) there was no increased susceptibility seen in studies submitted to the Agency, 2) there was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies, 3) there were no positive neurological effects in other toxicology studies; 4) the toxicology data base is complete; and 5) no concern is indicated by exposure assessment.

Specifically for **Methamidophos,** polyneuropathy was observed in hens at high doses, as well as the occurrence of delayed peripheral neuropathy in humans (through accidental occupational poisoning, suicide attempts, or ingestion of contaminated vegetables) as reported in the open literature.

Specifically for **Isofenphos,** delayed neuropathy was observed in an agricultural worker exposed to multiple pesticides including Isofenphos (as reported in the open literature), as well as concern for a number of poisoning incidents involving children (ages $\leq$ 5) reported by the Poison Control Center (1985-92 data).

For both pesticides, these concerns "triggered" the requirement for a developmental neurotoxicity study which in turn will provide additional data (e.g., potential increased susceptibility, effects on the development of the fetal nervous system, etc.). For Isofenphos, the developmental neurotoxicity study was requested by the FQPA Safety Factor Committee.

Specifically for **Dichlorvos (DDVP),** decreased brain weights in guinea pig fetuses was reported in the open literature. Additionally, there is concern for uncertainty in the chemical specific residential exposure data which warrants the FQPA safety factor. The Committee, however, determined that the 10x factor can be **reduced to 3x** because: 1) there was no increased susceptibility seen in studies submitted to the Agency, 2) there was no evidence of abnormalities in the development of the fetal nervous system in pre/postnatal studies or concern for positive neurological effects in other toxicology studies; and 3) the toxicology data base is complete.

In addition, the HIARC determined that a prenatal developmental toxicity study in guinea pigs is necessary to confirm the findings of the literature study; and therefore, the requirement of developmental neurotoxicity study is placed in reserve status pending the results of the aforementioned study.

iii. <u>FQPA Safety Factor Retained (10x)</u>

For **Cadusafos, Chlorpyrifos, Methyl Parathion, Oxydemeton-methyl, Tribuphos and Trichlorfon**, the FQPA safety factor of **10x** is **retained.**

The reasons for retaining the FQPA safety factor (10x) are based on: data gaps for <u>all three</u> neurotoxicity studies (1 pesticide); evidence of increased susceptibility (2 pesticides); concern for heritable effects (1 pesticide); evidence of neuropathology, as well as data gaps for neurotoxicity studies (1 pesticide); and evidence of neuropathology, data gaps for neurotoxicity and prenatal developmental toxicity studies (1 pesticide).

In general, hazard (based on the neurotoxicity, developmental, and reproductive toxicity studies) and exposure (dietary, drinking water, and residential) assessments indicate:

(a) In prenatal developmental toxicity studies following *in utero* exposure in rats and rabbits, there was no evidence of developmental effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses.

(b) In the pre/post natal two-generation reproduction study in rats, there was no evidence of enhanced susceptibility in pup when compared to adults (i.e., effects noted in offspring occurred at maternally toxic doses or higher).

(c) There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies submitted to the Agency.

(d) Adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess dietary and residential exposure and to provide a screening level drinking water exposure assessment.

Specifically for **Cadusafos,** there are data gaps for all three neurotoxicity studies (i.e., acute delayed in hens as well as acute and subchronic studies in rats) which places the requirement of a developmental neurotoxicity study in reserve status.

Specifically for **Chlorpyrifos** and **Methyl parathion,** in studies conducted at various scientific laboratories and reported in the open literature, neuropathology was observed in animals and/or humans, and evidence of increased susceptibility was seen in prenatal developmental toxicity studies in rats following oral, subcutaneous and/or intraperitoneal administrations. Although the subcutaneous and intraperitoneal routes of exposure are not traditional (i.e., oral), the Committee determined that the demonstration of increased susceptibility, as well as occurrence of neuropathology warrants the 10x safety factor. Also, these concerns result in the requirement of a developmental neurotoxicity study for both of these pesticides. *Note: The Agency acknowledges the recent receipt of a developmental neurotoxicity study for Chlorpyrifos which is currently under review.*

Specifically for **Oxydemeton methyl** there is concern for heritable effects as demonstrated in an *in vivo* mouse spot test. This test was positive for the induction of somatic cell mutations following intrauterine exposure of embryos. This adverse effect is clearly associated with the developing embryos thus warranting the 10x safety factor. A reproducible, concentration-dependent increase in mutation was seen at doses lower than the level causing maternal toxicity. In addition, there was valid evidence of DNA strand breaks in rat testes cells in an *in vitro* alkaline elution assay (not confirmed *in vivo*). Based on these concerns, the HIARC required a mouse specific locus test (this requirement was "triggered"by the positive mouse spot test).

Specifically for **Tribuphos,** OPIDN and neuropathology was observed following repeated dermal applications in hens, ocular effects and neuropathology were also seen in several species. In addition, there are data gaps for all three neurotoxicity studies. The concern for the effects seen after dermal exposure, in conjunction with the data gaps resulted in the requirement of a developmental neurotoxicity study.

Specifically for **Trichlorfon,** the safety factor is retained based on a number of factors including occurrence of neuropathology, as well as the presence of data gaps. Neurotoxicity concerns include the presence of OPIDN and neuropathology in hens, as well as decrease in brain weights in guinea pig fetuses in a prenatal developmental toxicity study identified in open literature. Data gaps include acute and subchronic neurotoxicity studies in rats and a prenatal developmental toxicity study in rats. These factors resulted in the requirement of a prenatal developmental toxicity study in guinea pigs (to verify the findings reported in the open literature). The developmental neurotoxicity study in rats is

placed in reserve status pending the results of the developmental toxicity study in the guinea pigs.

For **Chlorpyrifos-methyl, Dicrotophos, and Temephos** the FQPA safety factor is **retained** solely because of the inadequacy of the toxicology data base which precluded an evaluation of potential enhanced susceptibility to infants and children.

iv. FQPA Safety Factor Not Determined

An FQPA safety factor could not be determined for: **Fonofos**, since cancellation proceedings are in place for this pesticide; and **Isazophos-methyl**, for which there are no toxicology or exposure data available.

v. FQPA Safety Factor Not Applicable

An FQPA safety factor is not applicable to **Sulfotepp** since the only registered use is for greenhouses and there is no potential for exposure via the dietary, drinking water, or residential routes.

3. Application of the FQPA Safety Factor

For most of the organophosphates, the FQPA safety factor recommendations result from datagaps in the toxicology data requirements. The lack of a complete database encompasses the general population and is not limited to any one subpopulation.

For those organophosphates that require a developmental neurotoxicity study, the results from this study may be used in selecting endpoints that are applicable to risk assessments for all population groups.

When a developmental neurotoxicity study is required, it is generally recognized that the developmental effects seen in this study are considered to be "acute" effects and thus relevant for acute dietary risk assessment since it is presumed that developmental effects may arise from a single exposure. However, the results from this study may also be applicable for chronic dietary risk assessments because: 1) an extended dosing regimen (day 6 of gestation to day 10 postnatal) is used in the study; 2) developmental effects can occur at doses lower than those that induce chronic effects; and 3) adverse effects on human development can occur from birth through adolescence (long term process). Thus, the uncertainty related to the absence of a developmental neurotoxicity study makes it appropriate to apply a FQPA safety factor for acute and chronic dietary and non-dietary risk assessments for the general population including infants and children.

The FQPA safety factors are relevant for acute and chronic dietary risk assessments since the endpoints are based on plasma, red blood cell, and/or brain cholinesterase inhibition seen following single (acute) and/or repeated (chronic) exposures. Furthermore, it is also applied when performing residential (dermal and inhalation) exposure risk assessments, which utilize the oral endpoints with appropriate absorption factors for route-to-route extrapolation.

V. COMBINED UNCERTAINTY FACTORS FOR RISK ASSESSMENT

In risk assessment calculations, the FQPA safety factor recommendations must be considered along with the conventional Uncertainty Factors (i.e., 10x for interspecies extrapolation and 10x for intraspecies variability), and any additional Uncertainty Factors (UFs) assigned by the HIARC for various toxicological considerations. Examples of such considerations include the use of a LOEL when a NOEL was not established in the critical study or the use of a single sex human study. Presented below are the conventional Uncertainty Factors, the additional Uncertainty Factors assigned as needed by HIARC, the FQPA safety factor, and the resulting combined factors.

PESTICIDE	EXPOSURE SCENARIO	CONVEN-TIONAL FACTOR	ADDITIONAL UNCERTAINTY FACTOR (REASONS)	FQPA FACTOR	COMBINED FACTOR
Acephate	All[1]	100	No additional factor required	1	100
Azinphos-methyl	Acute Chronic No residential uses	100 100	3 (use of LOEL) No additional factor required	1	300 100
Bensulide	All	100	No additional factor required	1	100
Cadusafos	Acute Chronic No residential uses	100	No additional factor required	10	1000
Chlor-ethoxyfos	Acute Chronic No residential uses	100	No additional factor required	1	100
Chlorpyrifos	All	10	No additional factor required	10	100
Coumaphos	Acute Chronic No residential uses	100	No additional factor required	3	300
Diazinon	Acute Chronic Residential, Dermal[2] Residential, Inhalation[3]	100 10 10 100	No additional factor required 3 (NOEL/LOEL and one sex) [4] 3 (NOEL/LOEL and one sex) 3 (use of a LOEL)	1	100 30 30 300
Dimethoate	All	100	No additional factor required	1	100

[1] "All" indicates acute dietary, chronic dietary, and residential exposure scenarios.

[2] For all time periods (Short-, Intermediate-, and Long-Term) unless otherwise stated.

[3] For all time periods (Short-, Intermediate-, and Long-Term) unless otherwise stated.

[4] Diazinon: closeness of NOEL/LOEL established in the study.

PESTICIDE	EXPOSURE SCENARIO	CONVEN-TIONAL FACTOR	ADDITIONAL UNCERTAINTY FACTOR (REASONS)	FQPA FACTOR	COMBINED FACTOR
Disulfoton	All	100	No additional factor required	3	300
DDVP	Acute	10	No additional factor required		30
	Chronic	100	No additional factor required		300
	Residential:			3	
	Short-Term, dermal	10	No additional factor required		30
	Intermediate, dermal	10	3 (use of a LOEL)		100
	Long-Term, dermal	NA	Not required/No use		NA
	Inhalation	100	No additional factor required		300
Ethion	Acute	10	No additional factor required		10
	Chronic	10	10 (use of a LOEL and other reasons)[5]	1	100
	No residential uses				
Ethoprop	Acute	100	No additional factor required	1	100
	Chronic				
	No residential uses				
Ethyl parathion	Acute	100	No additional factor required		100
	Chronic	100	3 (use of a LOEL)	1	300
	No residential uses				
Fenamiphos	Acute	100	3 (use of a LOEL)		300
	Chronic	100	No additional factor required	1	100
	No residential uses				
Fenitrothion	All	100	No additional factor required	1	100
Fenthion	Acute	10	No additional factor required		10
	Chronic	10	3(threshold NOEL/LOEL)	1	30
	No residential uses				

[5] A UF of 10 was necessary due to the lack of a NOEL in the critical (human) study and the possibility that brain cholinesterase could be inhibited at dose levels comparable to those causing plasma cholinesterase inhibition as demonstrated in animal studies.

PESTICIDE	EXPOSURE SCENARIO	CONVEN-TIONAL FACTOR	ADDITIONAL UNCERTAINTY FACTOR (REASONS)	FQPA FACTOR	COMBINED FACTOR
Isofenphos	Acute	100	3 (use of a LOEL)		1000
	Chronic	100	No additional factor required		300
	Residential, Dermal and			3	
	Inhalation: Short-Term	100	3 (use of a LOEL)		1000
	Intermediate and Long-Term	100	No additional factor required		300
Malathion	Acute	100	No additional factor required		100
	Chronic	100	No additional factor required		100
	Residential:			1	
	Dermal (all time periods)	100	No additional factor required		100
	Inhalation, Short-Term	100	No additional factor required		100
	Intermediate and Long-Term	100	3 (use of a LOEL)		300
Metho-midophos	Acute Chronic No residential uses	100	No additional factor required	3	300
Methidathion	Acute Chronic No residential uses	100	No additional factor required	1	100
Methyl parathion	Acute Chronic No residential uses	100	No additional factor required	10	1000
Naled	All	100	No additional factor required	1	100
Oxydemeton-methyl	Acute	100	3 (use of a LOEL)	10	3000
	Chronic	10	No additional factor required		100
	No residential uses				
Phorate	Acute Chronic No residential uses	100	No additional factor required	3	300
Phosmet	All	100	No additional factor required	3	300
Phostebupirim	Acute Chronic No residential uses	100	No additional factor required	3	300

PESTICIDE	EXPOSURE SCENARIO	CONVEN-TIONAL FACTOR	ADDITIONAL UNCERTAINTY FACTOR (REASONS)	FQPA FACTOR	COMBINED FACTOR
Pirimiphos-methyl	Acute Chronic No residential uses	10 10	No additional factor required 30 (use of a LOEL + data gaps) [6]	3	30 1000
Profenofos	Acute Chronic No residential uses	100	No additional factor required	1	100
Propetamphos	All	100	No additional factor required	1	100
Terbufos	Acute Chronic No residential uses	100	No additional factor required	3	300
Tetra-chlorvinphos	All	100	No additional factor required	1	100
Tribuphos	Acute Chronic No residential uses	100 100	No additional factor required No additional factor required	10	1000 1000
Trichlorfon	Acute Chronic Residential	10 100 100	No additional factor required No additional factor required No additional factor required	10	100 1000 1000

Attachment 6. Tolerance Reassessment Summary

(NOTE: This document is not available electronically)

[6] Pirimiphos-methyl: Data gaps exists for a chronic toxicity study in dogs and a chronic/carcinogenicity study in rats.

Attachment 7. Codex Harmonization

(NOTE: This document is not available electronically)

Attachment 8. Fenamiphos Anticipated Residues

March 22, 1999

MEMORANDUM

Subject: **Fenamiphos Anticipated Residues:** Revised Values Using Anticipated Residues, PDP and FDA Data. Chemical # 100601. Case # 0333. DP Barcode D253961.

From: Sarah Law, Chemist
Risk Characterization and Analysis Branch
Health Effects Division 7509C

Through: Steve Knizner, Branch Senior Scientist
Risk Characterization and Analysis Branch
Health Effects Division 7509C

To: Todd Peterson
Reregistration Branch II
Special Review and Reregistration Division 7508C

Fenamiphos (Ethyl 3-methyl-4-(methylthio)phenyl-1-(methylethyl) phosphoramidate) is an organophosphate insecticide/nematicide. Tolerances for residues of fenamiphos are expressed in terms of fenamiphos and its regulable metabolites fenamiphos sulfoxide and fenamiphos sulfone. HED has provided revised anticipated residues of fenamiphos (tolerance listings: CFR 40 §180.349) for acute and chronic risk for the following commodities: apples, bananas, oranges, grapes, raisins, peaches, cherries, brussels sprouts, cabbage, bok choy, eggplant, garlic, okra, peanuts, pineapples, raspberries, strawberries, asparagus, garden beets, non-bell peppers, cottonseed, eggplant, grapefruit, lemons, limes, tangerines and okra. See attached tables for details.

Out of 26,619 monitoring data samples from PDP (1994-1997) and FDA (1995-1997) for all of the commodities listed below, only three samples had detectable residues (2 from grapes and 1 from strawberries). Two detectable residues of the fenamiphos sulfoxide metabolite were found in grapes by PDP in1995 (both at 0.008 ppm); one detectable residue of fenamiphos (including metabolites) was found in a strawberry by FDA in 1995.

In general, when monitoring data were used to calculate anticipated residues (ARs), the AR used for dietary exposure assessment was based on whichever data set (PDP or FDA) gave the lowest AR for combined regulable residues of fenamiphos, when looking at three years of monitoring data.

Table 1. Tolerances, Percent Crop Treated and Anticipated Residues for Fenamiphos.

Commodity	**Current Tolerance (ppm)**	**Tolerance Reassessment (ppm)**[1]	**% Crop Treated**[2]	**Acute Anticipated Residue Value**	**Chronic Anticipated Residue Value**
Apples	0.25	0.25	1	0.015	0.015
Apple Juice (AR's based on residues on RAC, corrected for %ct)	0.25	0.25 (tolerance covered by the tolerance for the apple RAC)	1	0.00006 (AR RAC * Proc.Factor[4] * % ct) = (0.015 ppm *0.42*0.01)	0.015
Asparagus	0.02	0.02	2	0.015	0.015
Bananas	0.10	0.10	100	0.004	0.004
Beets, garden, roots	1.5	1.5	2	0.015	0.015
Beets, garden, tops	1.0	1.0	2	na	na
Bok Choy	0.5	0.5	11	0.015	0.015
Brussels Sprouts	0.10	0.05	29	0.015	0.015
Cabbage	0.10	0.10	11	0.014[3]	0.014[3]
Cherries	0.25	0.25	2	0.015	0.015
Cottonseed	0.05	0.05	1	0.009[3]	0.009[3]
Cottonseed Oil	0.05	0.05	1	0.009[3]	0.009[3]
Eggplant	0.1	0.1	2	0.008[3]	0.008[3]
Garlic	0.50	0.5	2	Use distribution of field trial data[3] and %ct	0.028[3]

Grapefruit Lemons Limes Oranges Tangerines	0.6 0.6 0.6 0.6 0.6	0.5 0.5 0.5 0.5 0.5	3 13 6 4 6	0.015 0.015 0.015 0.015 0.015	0.015 0.015 0.015 0.015 0.015
Citrus Juice (tolerance covered by the tolerance for the citrus RAC)	0.5	0.5	See above	0.015 0.015 0.015 0.015 0.015	0.015
Citrus oil	25.0	25.0	na	0.015	0.015
Grapes	0.1	0.1	10	0.015	0.015
Grapes Juice (tolerance covered by the tolerance for the grape RAC)	0.1	0.1	10	0.015	0.015
Raisins	0.3	0.3	10	0.015	0.015
Okra	0.30	0.30	2	0.015	0.015
Peaches	0.25	0.25	3	0.015	0.015
Peanuts (and peanut butter)	0.02	1.0	4	0.0017 (AR^3 * % ct) = (0.042 ppm * 0.04)	0.042[3]
Peanut Oil	0.02	1.0	100	0.00084 (AR^3 * % ct) = (0.021 ppm * 0.04)	0.021[3]
Pineapples	0.30	0.30	70	0.015	0.015
Raspberries	0.1	0.1	21	0.009[3]	0.009[3]
Strawberries	0.6	0.6	2	0.015	0.015
Kiwifruit	0.1	0.1	17	0.1	0.1
Peppers, non-bell	0.6	0.6	2	0.015	0.015

1: Reassessed Tolerances According to RED (J. Cruz, 3/08/99, D253943)
2: % Crop Treated Information from BEAD (J. Morales, 9/10/98, D248384)
3: Reregistration of Fenamiphos: Anticipated Residue Calculations (C. Olinger, 12/20/93, D185627)
4: Fenamiphos Anticipated Residues: Revised Values for Apple, Grape, Banana, and Orange Processed Commodities (C. Olinger, 02/10/95, D211782)

Apples

Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 1% of the apple crop is treated by fenamiphos. PDP data are available for apples from 1994, 1995 and 1996 and for apple juice from 1996 and 1997. No detectable residues of fenamiphos or its regulable metabolites were found. Additionally, FDA data are available for apples from 1995, 1996 and 1997. Again, no measurable residues were found.

Using the FDA data, supported by PDP data and based on ½ the weighted LOD for parent and metabolites, the anticipated residue for both acute and chronic dietary exposure analysis is 0.015 ppm for apples (the most conservative value). For apple juice, the tolerance is covered by the apple raw agricultural commodity (RAC). Therefore the chronic anticipated residue was 0.015 ppm for apple juice and 0.00006 ppm (Apple RAC * Processing Factor * % ct) for acute. The apple processing factor was 0.42 (C. Olinger, 02/10/95, D211782). Table 2 below summarizes these results.

Table 2. Summary of Apple Data.

Crop	Source of Data	Year	# of Samples	Reassessment Tolerance (ppm)	Detects	Range of LOD's (ppm)	½ Weighted LOD (ppm)	Rationale for Use of Monitoring Data
Apples	FDA - Parent + Metabolites	1995 1996 1997	226 249 251	0.25	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples = 726
Apples	PDP- Parent per se	1996	530	0.25	0	0.002-0.013	0.003	0 detects from one year of PDP data.
Apples	PDP- Parent + Metabolites	1994 1995	687 693	0.25	0 0	0.002-0.013 0.002-0.049	0.005 0.006	0 detects from two years of PDP data. Total samples = 1380

Apples	PDP- Fenamiphos Sulfoxide	1996	281	0.25	0	0.005-0.12	0.022	0 detects from one year of PDP data.
Apples	PDP- Fenamiphos Sulfone	1996	281	0.25	0	0.005-0.097	0.018	0 detects from one year of PDP data.
Apple Juice	PDP- Parent per se	1996 1997	177 683	N/A**	0 0	0.002-0.010 0.002-0.009	0.003 0.002	0 detects from two years of PDP data. Total samples = 860
Apple Juice	PDP- Fenamiphos Sulfoxide	1996 1997	99 394	N/A**	0 0	0.005-0.12 0.005-0.036	0.015 0.007	0 detects from two years of PDP data. Total samples = 493
Apple Juice	PDP- Fenamiphos Sulfone	1996 1997	99 513	N/A**	0 0	0.005-0.097 0.005-0.036	0.013 0.007	0 detects from two years of PDP data. Total samples = 612

* Note that the FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.
** Note that apple juice is covered by the tolerance for the apple raw agricultural commodity (RAC).

Bananas

Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 100% of the banana crop is treated by fenamiphos. PDP data are available from 1994 and 1995. No detectable residues of fenamiphos or its regulable metabolites were found. Additionally, FDA data are available from 1995, 1996 and 1997. Again, no measurable residues were found.

Using the PDP data and based on ½ the weighted LOD for parent and metabolites, the anticipated residue for both acute and chronic dietary exposure analysis is 0.004 ppm. Table 3 below summarizes these results.

Table 3. Summary of Banana Data.

Crop	**Source of Data**	**Year**	**# of Samples**	**Reassessment Tolerance (ppm)**	**Detects**	**Range of LOD's (ppm)**	**½ Weighted LOD (ppm)**	**Rationale for Use of Monitoring Data**
Bananas	PDP- Parent + Metabolites	1994 1995	640 483	0.1	0 0	0.002-0.013 0.002-0.013	0.004 0.004	0 detects from two years of PDP data. Total samples =1123
Bananas	FDA - Parent + Metabolites	1995 1996 1997	257 233 336	0.10	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples =826

* Note that the FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.

Citrus

Under the citrus category, PDP analyzes for oranges and orange juice; FDA analyzes for grapefruit, lemons, limes, oranges and tangerines. Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 4% of the orange crop, 3% of the grapefruit crop, 13% of the lemon crop, 6% of the lime crop, and 6% of the tangerine crop is treated by fenamiphos. PDP data are available from 1994 and 1995. No detectable residues of fenamiphos or its regulable metabolites were found. Additionally, FDA data are available from 1995, 1996 and 1997. Again, no measurable residues were found.

Using the FDA data, supported by PDP data and based on ½ the weighted LOD for parent and metabolites, the anticipated residue for both acute and chronic dietary exposure analysis is 0.015 ppm. The orange peel concentration factor is 2.2x; the orange juice reduction factor is 0.17x; the ratio of residues in pulp to whole fruit is 0.2x for oranges, lemons, limes, tangerines and grapefruit (C. Olinger, 1/26/94, D187029; C. Olinger, 2/10/95, D211782). The oragne processing factors were used for all citrus crops and juices. Table 4 below summarizes these results.

Table 4. Summary of Citrus Data.

Crop	Source of Data	Year	# of Samples	Reassessment Tolerance (ppm)	Detects	Range of LOD's (ppm)	½ Weighted LOD (ppm)	Rationale for Use of Monitoring Data
Citrus	FDA - Parent + Metabolites	1995 1996 1997	297 144 308	0.5	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples = 749
Oranges	PDP- Parent per se	1996	518	0.5	0	0.002-0.013	0.004	0 detects from one year of PDP data.
Oranges	PDP- Parent + Metabolites	1994 1995	683 691	0.5	0 0	0.002-0.011 0.002-0.049	0.004 0.006	0 detects from two years of PDP data. Total samples =1374
Oranges	PDP- Fenamiphos Sulfoxide	1996	271	0.5	0	0.005-0.022	0.023	0 detects from one year of PDP data
Oranges	PDP- Fenamiphos Sulfone	1996	399	0.5	0	0.005-0.097	0.026	0 detects from one year of PDP data.
Orange Juice	PDP- Parent per se	1997	692	N/A**	0	0.002-0.013	0.004	0 detects from one year of PDP data.
Orange Juice	PDP- Fenamiphos Sulfoxide	1997	325	N/A**	0	0.005-0.022	0.006	0 detects from one year of PDP data.
Orange Juice	PDP- Fenamiphos Sulfone	1997	626	N/A**	0	0.005-0.080	0.012	0 detects from one year of PDP data.

* Note that the FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.

** Note that orange juice (and all citris juice) is covered by the tolerance for the orange (or respective citrus) raw agricultural commodity (RAC).

Grapes

Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 10% of the grape crop is treated by fenamiphos. PDP data are available from 1994, 1995 and 1996. Two detectable residues of the fenamiphos sulfoxide metabolite were found out of the 1649 samples analyzed for fenamiphos sulfoxide by PDP in 1994-1996. The minimum/maximum values detected were 0.008/0.008 ppm. Note that this level is approximately one-half the level of the anticipated residue used in the chronic and acute exposure analysis (see below). Additionally, FDA data are available from 1995, 1996 and 1997. No measurable residues were found.

Using the PDP data and based on ½ the weighted LOD for parent and metabolites, the anticipated residue for both acute and chronic dietary exposure analysis is 0.015 ppm. Raisins are a sub-set of grapes. Table 5 below summarizes these results.

Table 5. Summary of Grape Data.

Crop	**Source of Data**	**Year**	**# of Samples**	**Reassessment Tolerance (ppm)**	**Detects (% with detection)**	**Range of LOD's (ppm)**	**½ Weighted LOD (ppm)**	**Rationale for Use of Monitoring Data**
Grapes	FDA - Parent + Metabolites	1995 1996 1997	248 225 146	0.1	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples = 619
Grapes	PDP- Parent per se	1996	525	0.10	0	0.002-0.009	0.003	0 detects from one year of PDP data.
Grapes	PDP- Parent + Metabolites	1994 1995	669 690	0.1	0 0	0.002-0.013 0.002-0.009	0.004 0.003	0 detects from two years of PDP data. Total samples =1359
Grapes	PDP- Fenamiphos Sulfoxide	1996	280	0.10	2 (0.7%)	0.005-0.022	0.003	2 detects from one year of PDP data. Both values detected were 0.008 ppm.

Grapes	PDP-Fenamiphos Sulfone	1996	280	0.10	0	0.005-0.020	0.006	0 detects from one year of PDP data.
Raisins	FDA - Parent + Metabolites	1995 1996 1997	13 13 14	0.3	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples = 40

* Note that the FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.

Peaches

Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 3% of the peach crop is treated by fenamiphos. PDP data are available from 1994, 1995, 1996 and 1997. No detectable residues of fenamiphos or its regulable metabolites were found. Additionally, FDA data are available from 1995, 1996 and 1997. Again, no measurable residues were found.

Using the FDA data, supported by the PDP data, and based on ½ the weighted LOD for parent and metabolites, the anticipated residue for both acute and chronic dietary exposure analysis is 0.015 ppm. Table 6 below summarizes these results.

Table 6. Summary of Peach Data.

Crop	Source of Data	Year	# of Samples	Reassessment Tolerance (ppm)	Detects (% with detection)	Range of LOD's (ppm)	½ Weighted LOD (ppm)	Rationale for Use of Monitoring Data
Peaches	FDA - Parent + Metabolites	1995 1996 1997	251 164 188	0.25	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples = 603
Peaches	PDP- Parent per se	1996 1997	324 756	0.25	0 0	0.002-0.013 0.002-0.013	0.004 0.004	0 detects from two years of PDP data. Total samples = 1080
Peaches	PDP- Parent + Metabolites	1994 1995	396 367	0.25	0 0	0.002-0.013 0.002-0.013	0.004 0.004	0 detects from two years of PDP data. Total samples =763
Peaches	PDP- Parent + Sulfoxide	1996 1997	165 369	0.25	0 0	0.005-0.08 0.005-0.022	0.006 0.007	0 detects from two years of PDP data. Total samples = 534
Peaches	PDP- Fenamiphos Sulfone	1996 1997	246 693	0.25	0 0	0.005-0.080 0.005-0.080	0.018 0.012	0 detects from two years of PDP data. Total samples = 534

* Note that the FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.

Cherries

Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 2% of the cherry crop is treated by fenamiphos. There are no PDP data available for cherries. FDA data are available from 1995, 1996 and 1997. No measurable residues were found.

Using the FDA data and based on ½ the weighted LOD for parent and metabolites, the anticipated residue for both acute and chronic dietary exposure analysis is 0.015 ppm. Table 7 below summarizes these results.

Table 7. Summary of Cherry Data.

Crop	**Source of Data**	**Year**	**# of Samples**	**Reassessment Tolerance (ppm)**	**Detects**	**Range of LOD's (ppm)**	**½ Weighted LOD (ppm)**	**Rationale for Use of Monitoring Data**
Cherries	FDA - Parent + Metabolites	1995 1996 1997	83 43 70	0.25	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples =196

* Note that the FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.

Brussels Sprouts, Cabbage and Bok Choy

Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 29% of the brussels sprout crop, 11% of the cabbage crop and 11% of the bok choy crop are treated by fenamiphos. There are no PDP data available for brussel sprouts, cabbage or bok choy. FDA data are available from 1996 for brussels sprouts and from 1995, 1996 and 1997 for cabbage and bok choy. No measurable residues were found.

Using the FDA data and based on ½ the weighted LOD for parent and metabolites, the anticipated residue for both acute and chronic dietary exposure analysis for brussels sprouts and bok choy is 0.015 ppm each. For cabbage, the acute and chronic anticipated residu e is 0.014 ppm (C. Olinger, 12/20/93, D185627). Table 8 below summarizes these results.

Table 8. Summary of Brussels Sprouts, Cabbage and Bok Choy Data.

Crop	**Source of Data**	**Year**	**# of Samples**	**Reassessment Tolerance (ppm)**	**Detects**	**Range of LOD's (ppm)**	**½ Weighted LOD (ppm)**	**Rationale for Use of Monitoring Data**
Brussels Sprouts	FDA - Parent + Metabolites	1996	7	0.05	0	N/A	0.015*	0 detects from one year of FDA data. Total samples =7
Cabbage	FDA - Parent + Metabolites	1995 1996 1997	54 83 78	0.01	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples =215
Bok Choy	FDA - Parent + Metabolites	1995 1996 1997	10 25 20	0.5	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples =55

* Note that the FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.

Eggplant

Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 2% of the eggplant crop is treated by fenamiphos. There are no PDP data available for eggplant. FDA data are available from 1995, 1996 and 1997. No measurable residues were found.

If FDA data and based on ½ the weighted LOD for parent and metabolites were used, the anticipated residue for both acute and chronic dietary exposure analysis would be 0.015 ppm (See Table 9 below). However, previous data shows that the acute and chronic anticipated residue is 0.008 ppm (C. Olinger, 12/20/93, D185627).

Table 9. Summary of Eggplant Data.

Crop	**Source of Data**	**Year**	**# of Samples**	**Reassessment Tolerance (ppm)**	**Detects**	**Range of LOD's (ppm)**	**½ Weighted LOD (ppm)**	**Rationale for Use of Monitoring Data**
Eggplant	FDA - Parent + Metabolites	1995 1996 1997	27 45 48	0.05	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples =120

* Note that the FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.

Garlic

Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 2% of the garlic crop is treated by fenamiphos. There are no PDP data available for garlic. FDA data are available from 1997; however not enough samples were taken to draw a conclusion (summarized below in Table 10).

The chronic anticipated residue was calculated as 0.04 ppm (C. Olinger, 12/20/93, D185627). For the acute dietary analysis, the entire distribution of residue field trial results will be used (along with % crop treated) in the Monte Carlo analysis (Summarized in Table 11).

Table 10. Summary of Garlic Data.

Crop	Source of Data	Year	# of Samples	Reassessment Tolerance (ppm)	Detects	Range of LOD's (ppm)	½ Weighted LOD (ppm)	Rationale for Use of Monitoring Data
Garlic	FDA - Parent + Metabolites	1997	1	0.1	0	N/A	0.015*	0 detects from one year of FDA data. Total samples =1

* Note that the FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.

The distribution of field trial results (Summarized in Table 11) for the acute dietary exposure assessment will be used.

Table 11. Summary of Garlic Field Trial Data.

Field Trial Detection Values (ppm)	Source of Data	# of Samples	Number of Detects	Acute Anticipated Residue Value	Rationale for Use of Crop Field Trials
0.01, 0.26, 0.01, 0.03, 0.01, 0.08, 0.03, 0.01, 0.04, 0.01, 0.01, 0.02	MRID # 153458	12	12	Entire Distribution Used	An unsubstantial number of PDPand/or FDA data values were monitored.

Kiwifruit

Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 17% of the kiwifruit crop is treated by fenamiphos. There are no PDP data available for kiwifruit. FDA data are available from 1995, 1996 and 1997. No measurable residues were found; however not enough samples were taken to draw a conclusion. Therefore the reassessed tolerance of 0.1 ppm was used for the acute and chronic anticipated residue. Table 12 below summarizes the FDA results.

Table 12. Summary of Kiwifruit Data.

Crop	**Source of Data**	**Year**	**# of Samples**	**Reassessment Tolerance (ppm)**	**Detects (% with detection)**	**Range of LOD's (ppm)**	**½ Weighted LOD (ppm)**	**Rationale for Use of Monitoring Data**
Kiwifruit	FDA - Parent + Metabolites	1995 1996 1997	20 15 28	0.1	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples = 63

* Note that the FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.

Okra

Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 2% of the okra crop is treated by fenamiphos. There are no PDP data available for okra. FDA data are available from 1995, 1996 and 1997. No measurable residues were found.

Using the FDA data and based on ½ the weighted LOD for parent and metabolites, the anticipated residue for both acute and chronic dietary exposure analysis is 0.015 ppm. Table 13 below summarizes these results.

Table 13. Summary of Okra Data.

Crop	**Source of Data**	**Year**	**# of Samples**	**Reassessment Tolerance (ppm)**	**Detects**	**Range of LOD's (ppm)**	**½ Weighted LOD (ppm)**	**Rationale for Use of Monitoring Data**
Okra	FDA - Parent + Metabolites	1995 1996 1997	41 30 34	0.3	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples =105

* Note that the FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.

Peanuts

Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 4% of the peanut crop is treated by fenamiphos. There are no PDP data available for peanut. FDA data are available from 1996 and 1997. No measurable residues were found; however not enough samples were taken to draw a conclusion. Table 14 below summarizes the FDA results.

The chronic anticipated residue was calculated as 0.042 ppm (C. Olinger, 12/20/93, D185627). For the acute dietary analysis, the chronic anticipated residue multiplied by % crop treated will be used (0.042 ppm * 0.04 = 0.0017 ppm) in the Monte Carlo analysis.

The chronic and acute anticipated residue for peanut oil was calculated in the same manner as peanuts; howerver the chronic value for peanut oil is 0.021 ppm (C. Olinger, 12/20/93, D185627). The acute value for peanut oil is 0.00084 ppm.

Table 14. Summary of Peanut Data.

Crop	**Source of Data**	**Year**	**# of Samples**	**Reassessment Tolerance (ppm)**	**Detects**	**Range of LOD's (ppm)**	**½ Weighted LOD (ppm)**	**Rationale for Use of Monitoring Data**
Peanuts	FDA - Parent + Metabolites	1996 1997	2 1	1.0	0 0	N/A	0.015*	0 detects from two years of FDA data. Total samples =3

* Note that the FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.

Pineapples

Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 70% of the pineapple crop is treated by fenamiphos. There are no PDP data available for pineapple. FDA data are available from 1995, 1996 and 1997. No measurable residues were found.

Using the FDA data and based on ½ the weighted LOD for parent and metabolites, the anticipated residue for both acute and chronic dietary exposure analysis is 0.015 ppm. Table 15 below summarizes these results.

Table 15. Summary of Pineapple Data.

Crop	**Source of Data**	**Year**	**# of Samples**	**Reassessment Tolerance (ppm)**	**Detects**	**Range of LOD's (ppm)**	**½ Weighted LOD (ppm)**	**Rationale for Use of Monitoring Data**
PineappleS	FDA - Parent + Metabolites	1995 1996 1997	70 80 92	0.3	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples =242

* Note that the FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.

Raspberries

Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 21% of both the red and black raspberry crop is treated by fenamiphos. There are no PDP data available for raspberry. FDA data are available from 1995, 1996 and 1997. No measurable residues were found.

If FDA data and based on ½ the weighted LOD for parent and metabolites were used, the anticipated residue for both acute and chronic dietary exposure analysis would be 0.015 ppm (See Table 16below). However, previous data shows that the acute and chronic anticipated residue is 0.009 ppm (C. Olinger, 12/20/93, D185627), which is a lower value than calculated from FDA data.

Table 16. Summary of Raspberry Data.

Crop	**Source of Data**	**Year**	**# of Samples**	**Reassessment Tolerance (ppm)**	**Detects**	**Range of LOD's (ppm)**	**½ Weighted LOD (ppm)**	**Rationale for Use of Monitoring Data**
Raspberries	FDA - Parent + Metabolites	1995 1996 1997	86 89 126	0.1	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples =301

* Note that the FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.

Strawberries

Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 2% of the strawberry crop is treated by fenamiphos. There are no PDP data available for strawberry. FDA data are available from 1995, 1996 and 1997. One sample with a measurable residue was found at 0.97 ppm. Note that this is a violative sample (the tolerance for strawberries is 0.6 ppm).

Using the FDA data and based on ½ the weighted LOD for parent and metabolites, the anticipated residue for both acute and chronic dietary exposure analysis is 0.015 ppm. Table 17 below summarizes these results.

Table 17. Summary of Strawberry Data.

Crop	**Source of Data**	**Year**	**# of Samples**	**Reassessment Tolerance (ppm)**	**Detects**	**Range of LOD's (ppm)**	**½ Weighted LOD (ppm)**	**Rationale for Use of Monitoring Data**
Strawberries	FDA - Parent + Metabolites	1995 1996 1997	170 144 115	0.6	1 0 0	N/A	0.015*	1 detects from three years of FDA data. Total samples =4 Residue average = 0.97 ppm.

* Note that the FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.

Asparagus

Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 2% of the asparagus crop is treated by fenamiphos. There are no PDP data available for asparagus. FDA data are available from 1995, 1996 and 1997. No measurable residues were found.

Using the FDA data and based on ½ the weighted LOD for parent and metabolites, the anticipated residue for both acute and chronic dietary exposure analysis is 0.015 ppm. Table 18 below summarizes these results.

Table 18. Summary of Asparagus Data.

Crop	**Source of Data**	**Year**	**# of Samples**	**Reassessment Tolerance (ppm)**	**Detects (% with detection)**	**Range of LOD's (ppm)**	**½ Weighted LOD (ppm)**	**Rationale for Use of Monitoring Data**
Asparagus	FDA - Parent + Metabolites	1995 1996 1997	107 120 121	0.02	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples =348

* Note that thd FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.

Garden Beets

Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 2% of the garden beet crop is treated by fenamiphos. There are no PDP data available for garden beets. FDA data are available from 1995, 1996 and 1997. No measurable residues were found.

Using the FDA data and based on ½ the weighted LOD for parent and metabolites, the anticipated residue for both acute and chronic dietary exposure analysis is 0.015 ppm. Table 19 below summarizes these results.

Table 19. Summary of Garden Beet Data.

Crop	**Source of Data**	**Year**	**# of Samples**	**Reassessment Tolerance (ppm)**	**Detects (% with detection)**	**Range of LOD's (ppm)**	**½ Weighted LOD (ppm)**	**Rationale for Use of Monitoring Data**
Garden Beets, Roots	FDA - Parent + Metabolites	1995 1996 1997	21 29 27	1.5	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples = 77
Garden Beets, Tops	FDA - Parent + Metabolites	1995 1996 1997	4 1 6	1.0	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples = 11

* Note that the FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.

Peppers, Non-Bell

Based on the latest % crop treated information (J. Morales, 9/10/98, D248384), BEAD indicates that 2% of the non-bell pepper crop is treated by fenamiphos. There are no PDP data available for non-bell peppers. FDA data are available from 1995, 1996 and 1997. No measurable residues were found.

Using the FDA data and based on ½ the weighted LOD for parent and metabolites, the anticipated residue for both acute and chronic dietary exposure analysis is 0.015 ppm. Tables 20 below summarizes these results.

Table 20. Summary of Non-Bell Pepper Data.

Crop	**Source of Data**	**Year**	**# of Samples**	**Reassessment Tolerance (ppm)**	**Detects (% with detection)**	**Range of LOD's (ppm)**	**½ Weighted LOD (ppm)**	**Rationale for Use of Monitoring Data**
Peppers, non-bell	FDA - Parent + Metabolites	1995 1996 1997	262 273 227	0.6	0 0 0	N/A	0.015*	0 detects from three years of FDA data. Total samples =762

* Note that the FDA limit of detection (LOD) for fenamiphos and its regulable metabolites are 0.01 ppm each.

Cotton

Cotton is not monitored for by FDA or PDP. However, previous data shows that the acute and chronic anticipated residue is 0.009 ppm (C. Olinger, 12/20/93, D185627).

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